ROUTING AND ACTION
MEMORANDUM

ROUTING

TO: (1) Chemical Sciences Division (Parker, James)

Report is available for review

(2) Proposal Files Proposal No.: 72450-CH-REP

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INSTITUTION: Jackson State University

PRINCIPAL INVESTIGATOR: Alamgir Hossain

TYPE REPORT: Interim Progress Report

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PERIOD COVERED: 04-Oct-2018 through 31-July-2019

TITLE:

ACTION TAKEN BY DIVISION

(x) Report has been reviewed for technical sufficiency and IS [x] IS NOT [ ] satisfactory.

(x) Material has been given an OPSEC review and it has been determined to be non sensitive and, except for manuscripts and progress reports, suitable for public release.

Approved by SSL\JAMES.KENNETH.PARKER on 3/10/20 4:03PM

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REPORT DOCUMENTATION PAGE

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30-09-2019	Interim Progress Report	4-Oct-2018 - 31-Jul-2019

4. TITLE AND SUBTITLE

Supramolecular Recognition and Sensing of Hazardous Anionic Contaminants with Urea and Thiourea Based Synthetic Receptors

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6. AUTHORS

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Jackson State University
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12. DISTRIBUTION AVAILIBILITY STATEMENT

Approved for public release; distribution is unlimited.

13. SUPPLEMENTARY NOTES

The views, opinions and/or findings contained in this report are those of the author(s) and should not contrued as an official Department of the Army position, policy or decision, unless so designated by other documentation.

14. ABSTRACT

15. SUBJECT TERMS

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UU	UU	UU	UU		19b. TELEPHONE NUMBER 601-979-3748

RPPR Interim Progress Report
as of 10-Mar-2020

Agency Code:

Proposal Number: 72450CHREP **Agreement Number: W911NF-19-1-0006**
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DUNS Number: 044507085 EIN: 646000507

Report Date: 31-Aug-2019 Date Received: 30-Sep-2019
Interim Progress Report for Period Beginning 04-Oct-2018 and Ending 31-Jul-2019

Title: Supramolecular Recognition and Sensing of Hazardous Anionic Contaminants with Urea and Thiourea Based Synthetic Receptors
Begin Performance Period: 04-Oct-2018 **End Performance Period:** 03-Oct-2021
Report Term: 1-Annual

Submitted By: Alamgir Hossain Email: alamgir.hossain@jsums.edu
Phone: (601) 979-3748

Distribution Statement: 1-Approved for public release; distribution is unlimited.

STEM Degrees: 3 **STEM Participants:** 10

Major Goals: (1) Synthesize a new series of urea/thiourea functionalized receptors containing variable dimensions, sizes, and spacers.
(2) Investigate molecular interactions of the proposed receptors with selected anions (uranate, perchlorate, tungstate, sulfate, nitrate, cyanide, iodide and fluoride) using NMR, UV-Vis, fluorescence spectroscopy, and X-ray crystallography.
(3) Study the liquid-liquid extraction of anions using gravimetric method, and spectroscopic analysis.
(4) Calculate binding energies and electronic spectra using molecular modeling to gain a theoretical understanding of intermolecular interactions.

Accomplishments: 1. Synthesis of a thiourea-based tripodal urea for naked-eye detection of sulfate via fluoride displacement assay

A thiourea-based tripodal receptor substituted with 3-nitrophenyl groups has been studied for the binding of anions by 1H NMR and UV-Vis titrations in DMSO. The receptor has been shown to bind an anion, showing the strong selectivity for sulfate. A competitive colorimetric assay in the presence of fluoride suggests that the bound fluoride can be displaced by sulfate, exhibiting a visible color change.

2. Synthesis of electronically variable tris(3-aminopropyl)amine-based thiourea receptors for anions

Three thiourea electronically variable receptors have been synthesized and evaluated for their binding affinities for inorganic anions via proton NMR titration studies in solution. The receptors exhibited the strongest binding affinities for fluoride among halides and phosphate among oxoanions. Binding strengths among the receptors increased with the relative acidities of the aromatic spacer groups. Competitive binding assays revealed the selective binding trend for all of the receptors: fluoride > sulfate > dihydrogen phosphate.

3. Ditopic binding of halides by a m-nitrophenyl-functionalized hexaurea receptor

A tripodal-based hexaurea receptor 1 appended with m-nitrophenyl groups has been studied for halide binding by proton NMR, UV-Vis titrations, and high level density functional theory (DFT) calculations. As demonstrated by experimental and computational results, the receptor effectively binds a halide ion in a 1:2 binding mode showing the binding strength in the order of fluoride > chloride > bromide > iodide. The strongest affinity for fluorides is attributed to the best fit of two fluoride anions within the host's cavity. This is also supported by DFT calculations, showing that each anion is stabilized by six NH???F bonds - one at the inner cleft and other at the outer cleft.

Training Opportunities: The following students have been trained in the area of supramolecular chemistry and prepared to present their research results at scientific conferences. Several students have been awarded top places in the students' poster/oral competition.

Graduate students:

Corey R. Johnson: Corey R. Johnson is a final year Ph.D. student who has been involved in the synthesis and binding studies of acyclic thiourea-based receptors for anions. Corey has gained substantial experiences in synthetic works on target oriented molecules, and in operating NMR and UV-Vis and fluorescence spectroscopes. In addition, he has been trained in teaching of Inorganic Chemistry and Organic Chemistry at Jackson State University in undergraduate level courses. Corey has successfully defended his final dissertation, and is finishing his dissertation this Fall.

Bobby J. Portis: Bobby J. Portis is a third year Ph.D. student in the Hossain group. His research focuses on the synthesis and anion binding studies of hexa-functional urea receptors proposed in the DoD proposal. Bobby is investigating these compounds for halides and oxoanions by NMR spectroscopy. In order to gain mentoring experiences, Bobby was involved in training one summer high school Muhammad Nafis in Summer 2018. In addition of his own work, Bobby is also involved in mentoring two undergraduate students working in the Hossain Lab.

Tochukwu K. Egboluche: Tochukwu has joined the Hossain group this Fall (2019) as a Ph.D. student in chemistry and is being supported by the DoD grant. He is now involved in the design and synthesis of thioura-based receptors that will be studied by NMR and liquid-liquid extraction studies for selective binding of target anions proposed in the project.

Amber C. Gardner: Amber is supported by the DoD grant and is involved in the synthesis of macrocyclic-based receptors. She has been trained particularly in high dilution synthesis and several instrumental techniques including fluorescence and UV-Vis spectroscopes. Amber is now at her final stage in completing her M.Sc. degree, and will be awarded her degree in December 2019.

Brianna C. Ross: Brianna is a newly recruited M.Sc. student, who has started her work in the Hossain group. Brianna's work is focused on the macrocycle-based receptors that will be used for sensing of oxoanions.

Undergraduate students:

Alyssa E. Johnson: Alyssa worked in the Hossain groups for the Fall 2018 and Spring 2019 in the synthesis of a nitrophenyl-based tripodal thiourea and its binding studies for halides. She was trained in NMR titrations and colorimetric studies. During this time, she was mentored by Corey Johnson.

Destiny Nicholson: This student is now working with the graduate student, Bobby J. Portis. Destiny is involved in the synthesis of acyclic urea and is being trained in calculating binding data by non-linear regression analysis.

Jalah L. Carter: As an undergraduate student, Jalah has been working with Hossain group. She is currently being trained in colorimetric and UV-titration studies of a thiourea-based molecular receptor.

Jaylen Davis: Jaylen joined the Hossain group in Fall 2019, and is involved in high dilution synthesis of amine-based acycles and their characterization. He is linked with the graduate student, Amber Gardner.

Shaurya Swami: Shaurya is assigned to work on thiourea-based acyclic receptors and is linked to the graduate student Bobby Portis. He is currently being trained in UV-Vis titration and colorimetric studies.

High School student:

Muhammad Nafis: Muhammad was recruited from a local high school in the last summer and trained in the interdisciplinary research area of Supramolecular Chemistry during the period of June 01 – July 27, 2018. Based on his work, he already presented his research at scientific meeting and won first place in the poster presentation.

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Results Dissemination: Dr. Hossain and his group has shared and disseminated his research work with other scientists at the following scientific meetings and symposiums:

1. Hossain, M. A. Selective Recognition of Biologically Anions with Synthetic Receptors. Fifteenth international symposium on recent advances in environmental health research, Jackson, MS, Feb 17-20, 2019 (invited).
2. Hossain, M.A.; Rhaman, M.M.; Exploring transition metal complexes for selective recognition of biologically relevant anions. Annual Symposium of Mississippi Academy of Science, Hattiesburg, MS, Feb 21-22, 2019 (invited).
3. Portis, B.; Hasan, M.H.; Johnson, C.R.; Tandon, R.; Hossain, M.A. Ditopic binding of halides by a m-nitrophenyl-functionalized hexaurea receptor. Annual Symposium of Mississippi Academy of Science, Hattiesburg, MS, Feb 21-22, 2019.
4. Gardner, A.; Rhaman, M. M.; Hossain, M.A. Colorimetric detection of oxalate in water by indicator displacement assay at neutral pH. Annual Symposium of Mississippi Academy of Science, Hattiesburg, MS, Feb 21-22, 2019.
5. Johnson, C.R.; Johnson, A. E.; Gardner, A.C.; Emami, M.E.; Hossain, M.A. Selective binding studies of anions with a nitrophenyl-based tripodal thiourea. Annual Symposium of Mississippi Academy of Science, Hattiesburg, MS, Feb 21-22, 2019.
6. Gardner, A.; Rhaman, M. M.; Hossain, M.A. Colorimetirc Detection of Oxalate in Water by Indicator Displacement Assay at Neutral pH. Fifteenth international symposium on recent advances in environmental health research, Jackson, MS, Feb 17-20, 2019.
7. Portis, B.; Mirchi, A.; Hasan, M.H.; Johnson, C. R. Gardner, A. Leszczynski, J.; Tandon, R.; Hossain, M.A. Ditopic Binding of Halides by a M-Nitrophenyl-Functionalized Hexaurea Receptor. Fifteenth international symposium on recent advances in environmental health research, Jackson, MS, Feb 17-20, 2019.
8. Hossain, M. A.; Rhaman, M. M.; Hasan, M. H. Molecular recognition of biologically relevant anions with transition metal complexes. 256th ACS National Meeting & Exposition, Orlando, FL, Mar 31- Apr 4, 2019.
9. Hossain, M. A.; Portis, B.; Johnson, C. R.; Khansari, M. E.; Jahan, A.; Powell, D.R. Perfect C3 symmetric sulfate complex with a urea-based hexafunctional synthetic receptor. 257th ACS National Meeting & Exposition, San Diego, CA, Aug 25- 29, 2019.
10. Rhaman, M. M; Powell, D.R.; Hossain, M. A. Supramolecular assembly of uridine monophosphate (UMP) and thymidine monophosphate (TMP) with a dinuclear copper(II) receptor. 257th ACS National Meeting & Exposition, San Diego, CA, Aug 25- 29, 2019.
11. Nafis, M.; Portis, B..; Hossain, M. A. Urea and thiourea-based cleft receptors for anions. JSU-UCSB PREM Material Science Conference, July 24, 2019, Jackson, MS (Ist place in poster competition).

Plans Next Period: Synthesis: During the second year, it is planned to synthesized molecules varying functionalities (urea to thiourea), dimensionalities (monopodal to tripodal), and attached groups (electron-withdrawing and electron-donating groups). Attempts will be made to grow suitable crystals in order to understand structure-activity relationship in host-guest compelxes.

Binding studies: The synthesized molecules will be thoroughly studied for selective binding of anions by NMR titrations, Fluorescence and UV-Vis spectroscopes. In addition, the molecules will be investigated for extractions studies.

Molecular modeling. Molecular modeling will be performed to integrate experimental and theoretical data. Computer-aided molecular design will be used to determine structure-selectivity relationships.

Student training: Students will be provided training in fundamentals of the scientific method, laboratory safety, scientific ethics, and other standards of professional practice. In particular, newly recruited students will be trained both in research and teaching.

Publications/presentation. During the second year, it is planned to present research results at different scientific meetings and publish several publications in peer reviewed journals.

Honors and Awards: 1. Bobby Portis won the second place for the manuscript award in 2019 during the annual meeting of Mississippi Academy of Science in Hattiesburg, MS held on February 20-21, 2019.

2. Muhammad Nafis (high school student) won the first place for the poster presentation in summer 2018.

Protocol Activity Status:

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Technology Transfer: Nothing to Report

PARTICIPANTS:

Participant Type: PD/PI
Participant: Alamgir Hossain
Person Months Worked: 12.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: Graduate Student (research assistant)
Participant: Corey R Johnson
Person Months Worked: 12.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: Graduate Student (research assistant)
Participant: Bobby J Portis
Person Months Worked: 12.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: Graduate Student (research assistant)
Participant: Tochukwu K Egboluche
Person Months Worked: 1.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: Graduate Student (research assistant)
Participant: Amber C Gardner
Person Months Worked: 12.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: Graduate Student (research assistant)
Participant: Brianna C Brianna
Person Months Worked: 1.00 **Funding Support:**
Project Contribution:

International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: Undergraduate Student
Participant: Destiny Nicholson
Person Months Worked: 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: Undergraduate Student
Participant: Jalah L Carter
Person Months Worked: 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: Undergraduate Student
Participant: Jaylen Davis
Person Months Worked: 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: Undergraduate Student
Participant: Shaurya Swami
Person Months Worked: 2.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: Undergraduate Student
Participant: Alyssa E. Johnson
Person Months Worked: 9.00 **Funding Support:**
Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

Participant Type: High School Student
Participant: Muhammad Nafis
Person Months Worked: 2.00 **Funding Support:**

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Project Contribution:
International Collaboration:
International Travel:
National Academy Member: N
Other Collaborators:

CONFERENCE PAPERS:

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: Fifteenth international symposium on recent advances in environmental health research
Date Received: 30-Sep-2019 Conference Date: 17-Feb-2019 Date Published: 17-Feb-2019
Conference Location: Jackson, MS USA
Paper Title: Selective recognition of biologically relevant anions with synthetic receptors
Authors: Md Alamgir Hossain
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: Annual Symposium of Mississippi Academy of Science
Date Received: 30-Sep-2019 Conference Date: 21-Feb-2019 Date Published: 21-Feb-2019
Conference Location: Hattiesburg, MS
Paper Title: Ditopic binding of halides by a m-nitrophenyl-functionalized hexaurea receptor
Authors: Bobby Portis, Mohammad Hasan, Corey Johnson, Ritesh Tandon, Md Hossain
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: Annual Symposium of Mississippi Academy of Science, Hattiesburg
Date Received: 30-Sep-2019 Conference Date: 22-Sep-2019 Date Published: 22-Sep-2019
Conference Location: Hattiesburg, MS, USA
Paper Title: Colorimetirc detection of oxalate in water by indicator displacement assay at neutral pH
Authors: Amber Gardner, Md Rhaman, Md Hossain
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: Annual Symposium of Mississippi Academy of Science
Date Received: 30-Sep-2019 Conference Date: 22-Feb-2019 Date Published: 22-Feb-2019
Conference Location: Hattiesburg, MS, USA
Paper Title: Exploring transition metal complexes for selective recognition of biologically relevant anions
Authors: Md Hossain, Md Rhaman
Acknowledged Federal Support: **Y**

Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published
Conference Name: 256th ACS National Meeting & Exposition
Date Received: 30-Sep-2019 Conference Date: 31-Mar-2019 Date Published: 31-Mar-2019
Conference Location: Orlando, FL, USA
Paper Title: Molecular recognition of biologically relevant anions with transition metal complexes
Authors: Md Hossain, Md Rhaman, Mohammad Hasan
Acknowledged Federal Support: **Y**

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Publication Type: Conference Paper or Presentation **Publication Status:** 1-Published

Conference Name: 257th ACS National Meeting & Exposition

Date Received: 30-Sep-2019 Conference Date: 25-Aug-2019 Date Published: 25-Aug-2019

Conference Location: San Diego, CA, USA

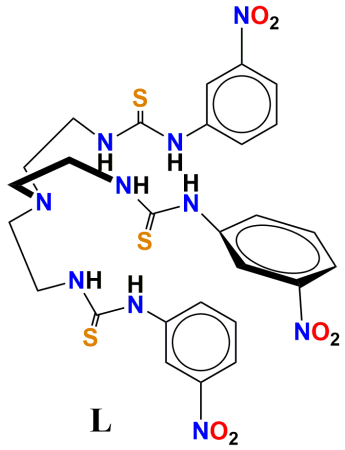
Paper Title: A perfect C3 symmetric sulfate complex a urea-based hexafunctional synthetic receptor

Authors: Md Hossain, Bobby Portis, Maryam Khansari, Corey Johnson, Afsana Jahan, Douglas Powell

Acknowledged Federal Support: **Y**

1. Synthesis of a Thiourea-based Tripodal Urea for Naked-Eye Detection of Sulfate via Fluoride Displacement Assay

A thiourea-based tripodal receptor L substituted with 3-nitrophenyl groups has been studied for the binding of anions by ^{1}H NMR and UV-Vis titrations in DMSO-d_6. The receptor has been shown to bind an anion, showing the strong selectivity for sulfate. A competitive colorimetric assay in the presence of fluoride suggests that the bound fluoride can be displaced by sulfate, exhibiting a visible color change.



L

NMR titration studies: ^{1}H NMR titrations of **L** were performed to evaluate its binding affinity for a variety of anions (F^-, Cl^-, Br^-, I^-, ClO_4^-, NO_3^-, $H_2PO_4^-$, HSO_4^-, and SO_4^{2-}) using their tetrabutylammonium salts in DMSO-d_6. Figure 1 shows the stacking of ^{1}H NMR spectra as obtained from the titration of **L** with SO_4^{2-} (0-10 eq.). In the ^{1}H NMR spectrum of **L**, one NH proton is observed at 10.01 (H1) ppm and the other one at 7.95 (H2) ppm. The addition of SO_4^{2-} to **L** resulted in a significant downfield shift of both NH signals ($\Delta\delta$= 1.49 ppm for H1 and $\Delta\delta$= 1.81 ppm for H2) with a sharp saturation at a 1:1 ratio (Figure 1), demonstrating strong interactions of the receptor and sulfate. Similar downfield shifts in the NH signals, but to a lesser extent, were also observed for HSO_4^- ($\Delta\delta$= 0.72 ppm for H1 and $\Delta\delta$= 0.71 ppm for H2), Cl^- ($\Delta\delta$= 0.61 ppm for H1 and $\Delta\delta$= 0.38 ppm for H2) and Br^- ($\Delta\delta$= 0.09 ppm for H1 and $\Delta\delta$= 0.06 ppm for H2) at the end of titrations. The NH signals of **L** were shown to be broadened and eventually disappeared upon the addition of $H_2PO_4^-$. In this case, CH signals were used to calculate the binding constant. However, for I^-, NO_3^- and ClO_4^-, a negligible change in the NMR signals was observed. The binding constants of **L** for these anions were determined from a nonlinear regression analysis of the progressive changes of NH or CH signals with a 1:1 binding model. The binding data are listed in Table 1, showing that the receptor binds strongly to SO_4^{2-}, with an association constant larger than 10^4 M^{-1} (Table 1).

In contrast, upon the addition of fluoride to **L**, a new set of NMR signals appeared at downfield via a slow proton exchange between the free receptor and the complex. The signals of the free

receptor disappeared completely upon the addition of one equivalent of fluoride (Figure 2). The distinct downfield shift of NH signals in our receptor is consistent with the formation of a hydrogen-bonded complex. For further clarification, a control experiment was carried out using OH^-, showing complete disappearance of NH signals due to the deprotonation of NH by highly basic hydroxide ions (**E**, Figure 2).

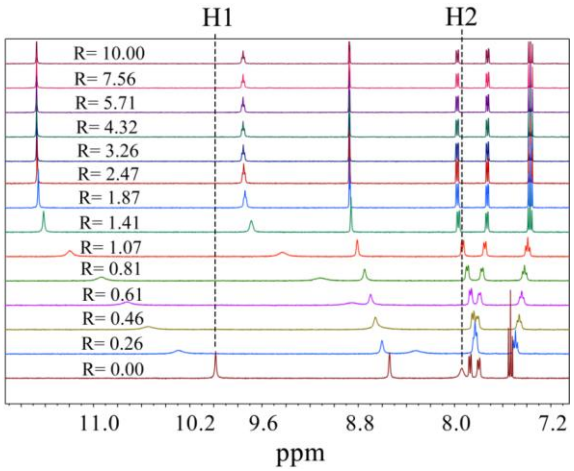


Figure 1. Partial ^{1}H NMR spectra of **L** (2 mM) showing changes in the NH chemical shifts with an increasing amount of SO_4^{2-} (20mM) in DMSO-d_6. (H1 = CSN*H*Ar and H2 = CH_2N*H*CS).

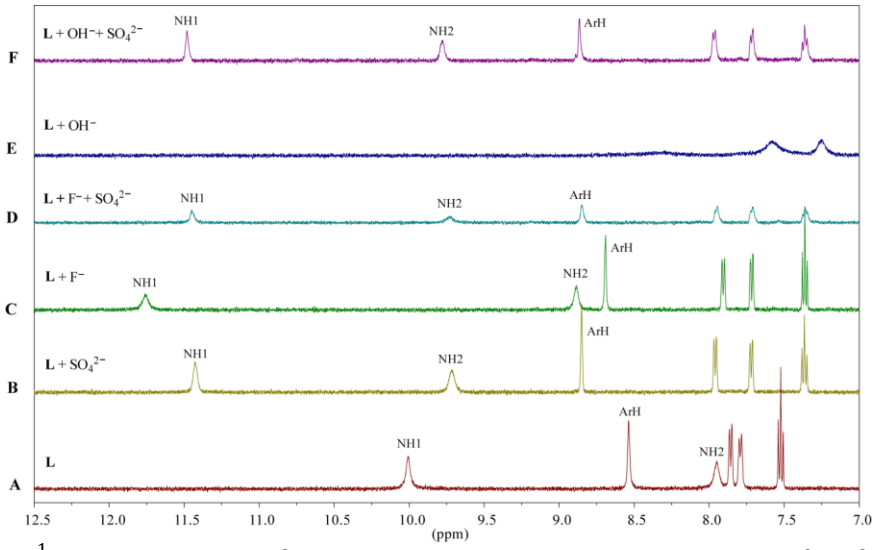


Figure 2. Partial ^{1}H NMR spectra of **L** showing changes in the chemical shifts after the addition of one equivalent of different anions in DMSO-d_6.

The binding constant for fluoride was calculated from the relative changes in the integrated intensity of NH signals for the free receptor and the complex, yielding a binding constant larger than 10^4 M^{-1}. In order to determine the selectivity of the receptor, competition experiments were performed in which sulfate was added to the receptor containing one equivalent of fluoride (**C**, Figure 2) or hydroxide (**E**, Figure 2) in DMSO-d_6. As shown in Figure 2, the ^{1}H NMR spectrum

of **L** containing an equivalent amount of fluoride and sulfate (**D**), or hydroxide and sulfate (**F**), resembles the spectrum of **L** containing one equivalent of sulfate (**B**), thus demonstrating the selectivity of the receptor for sulfate. The receptor also exhibits good interactions for Cl^-, HSO_4^-, and $H_2PO_4^-$ with association constants of 3.1, 2.9 and 3.0 (in log *K*), respectively. However, it does not show any appreciable affinity for I^-, NO_3^-, or ClO_4^-.

Table 1. Binding constants (log *K*) and binding energies (*E*) of the anions complexes of **L**.

Anion	Log K^a	Log K^b
F^-	> 4.0 [c]	5.1
Cl^-	3.1	3.2
Br^-	1.9	1.7
I^-	<1 [d]	<1 [e]
SO_4^{2-}	> 4.0	6.4
HSO_4^-	2.9	2.8
$H_2PO_4^-$	3.0	3.1
NO_3^-	<1 [d]	<1 [e]
ClO_4^-	<1 [d]	<1 [e]

[a] Determined by ^{1}H NMR titrations in DMSO-d_6; [b] determined by UV titrations in DMSO; [c] slow proton exchange; [d] no appreciable change was observed in ^{1}H NMR spectra; [e] no appreciable change was observed in UV spectra.

Colorimetric studies: The receptor was further investigated by naked eye colorimetric studies for anions in DMSO. As shown in Figure 3, a visible color change from pale yellow to orange was observed after the addition of one equivalent of fluoride to **L** (2 mM), indicating a different optical absorption spectrum of the $[\mathbf{L}F]^-$ complex. However, the color remained almost unchanged for other anions. A similar color change was reported previously due to the addition of fluoride to related receptors. In order to examine the visual selectivity, one equivalent of different anions was added separately to an orange solution of fluoride complex in DMSO. Interestingly, the color of $[\mathbf{L}F]^-$ was sharply changed to a pale yellow color (original color of the receptor) after the addition of sulfate. This observation suggests that sulfate can compete with fluoride for hydrogen bonding with NH groups, and displace the bound fluoride from the complex $[\mathbf{L}F]^-$ into solution, which is in agreement with NMR competition experiments (Figure 2). However, other anions are not strong enough to displace the bound fluoride, supporting the results of NMR and UV-Vis titrations. Thus, the fluoride-receptor complex serves as a colorimetric probe for visual identification of sulfate through *fluoride displacement assay*.

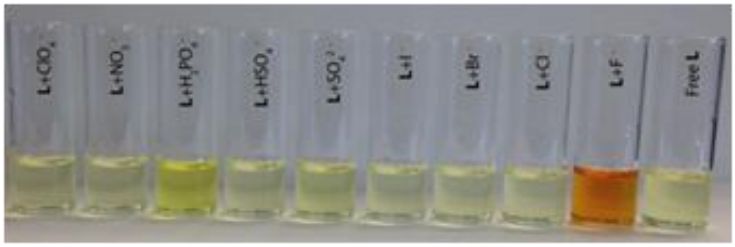


Figure 3. Colorimetric studies of the receptor **L** (2 mM) with one equivalent of different anions in DMSO.

Figure 4. Colorimetric studies of $[\mathbf{L}F]^-$ after the addition of one equivalent of different anions in DMSO, showing a visual color change for sulfate.

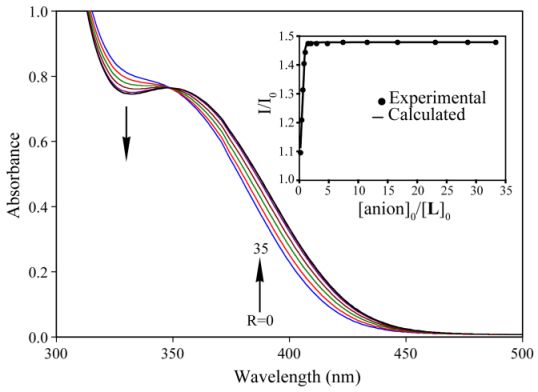


Figure 5. UV-Vis titration spectra showing the changes in absorption spectra of **L** (1.5×10^{-4} M) with an increasing amount of SO_4^{2-} (1.5×10^{-2} M) in DMSO (Inset showing the titration plot).

UV-Vis titration studies: UV-Vis titrations were also performed to investigate the interactions of the receptor with anions in DMSO. As shown in Figure 5, the addition of sulfate to a solution of **L** results in a systematic decrease in the absorbance with a red shift of the peak at 335 nm, suggesting the formation of a $[\mathbf{L}(SO_4)]^{2-}$ complex. The relative absorbance I/I_0 of **L** (where I_0 and I represent the absorbance of **L** before and after the addition of an anion, respectively) upon the gradual addition of SO_4^{2-} gave the best fit to a 1:1 binding mode yielding a binding constant of 6.40 (in log *K*). The host showed a similar spectral

change when it was titrated with dihydrogen phosphate. The addition of fluoride anion to **L** also showed a decrease in the absorption at 335 nm, but no appreciable shift was observed as compared to that for sulfate or phosphate. However, the naked-eye colorimetric study shows an orange color after the addition of just one equivalent of fluoride to the receptor in which the concentration of **L** was different (2 mM) than that used in UV titrations (0.15 mM). On the other hand, the addition of other anions to **L** solution does not induce an appreciable change in the absorption spectrum. This observation is fully consistent with colorimetric observations, showing no visible color change for Cl^-, Br^-, I^-, ClO_4^-, NO_3^-, and HSO_4^-.

2. Synthesis of Electronically Variable Tris(3-aminopropyl)amine-based Thiourea Receptors for anions

Three thiourea electronically variable receptors **L1-L3** have been synthesized and evaluated for their binding affinities for inorganic anions via ^{1}H NMR titration studies in solution. The receptors exhibited the strongest binding affinities for fluoride among halides and phosphate among oxoanions. Binding strengths among the receptors increased with the relative acidities of the aromatic spacer groups. Competitive binding assays revealed the selective binding trend for all of the receptors: fluoride > sulfate > dihydrogen phosphate.

Synthesis: We have synthesized the three receptors (**L1**-**L3**) of this study via a one-step reaction between tris(3-aminopropyl)amine and selected isothiocyanates in dichloromethane under reflux conditions (Figure 6). The aryl spacers were attached to the amine linker to investigate the effects of electronically variable aromatic substituents on the binding capabilities of this receptor series.

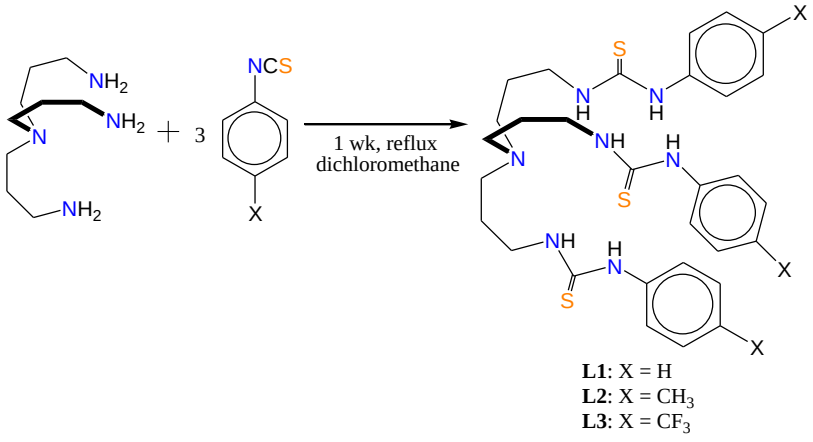


Figure 6. Synthesis of series **L**.

Binding studies: Screening assays were performed using proton NMR spectroscopy after the adding 1 equiv. of F^-, Cl^-, Br^-, I^-, HSO_4^-, SO_4^{2-}, $H_2PO_4^-$, ClO_4^-, and NO_3^- to **L1**, **L2**, and **L3** in DMSO-d_6 (**Figures 7-9)**. Substantial changes in the NH chemical shifts of each receptor were

observed only upon 1 equiv. addition of F^-, Cl^-, HSO_4^-, SO_4^{2-}, and $H_2PO_4^-$. For **L1**, the largest NH2 ($\Delta\delta$1.02) and NH1 shifts ($\Delta\delta$0.77) occurred upon addition of 1 equiv. of F^-. For **L2**, the largest shift NH2 ($\Delta\delta$ 0.55) and NH1 ($\Delta\delta$0.56) shifts occurred upon addition of $H_2PO_4^-$. For **L3**, the largest NH2 ($\Delta\delta$0.60) and NH1 shifts ($\Delta\delta$0.64) occurred upon addition of HSO_4^-.

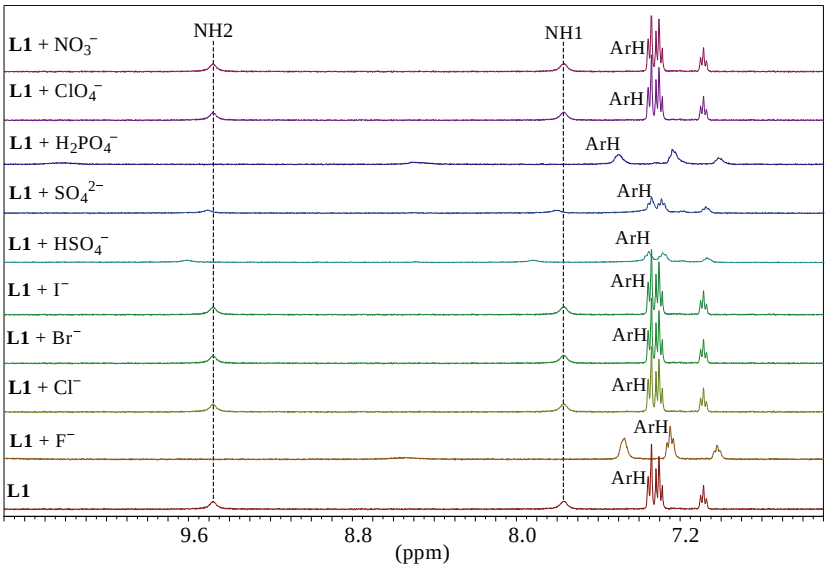


Figure 7. Partial ^{1}H NMR titration of **L1** (2 x 10^{-3} M) against 1 equiv. of various anions in DMSO-d_6. (NH2 = CSN*H*Ar, NH1 = CH_2N*H*CS).

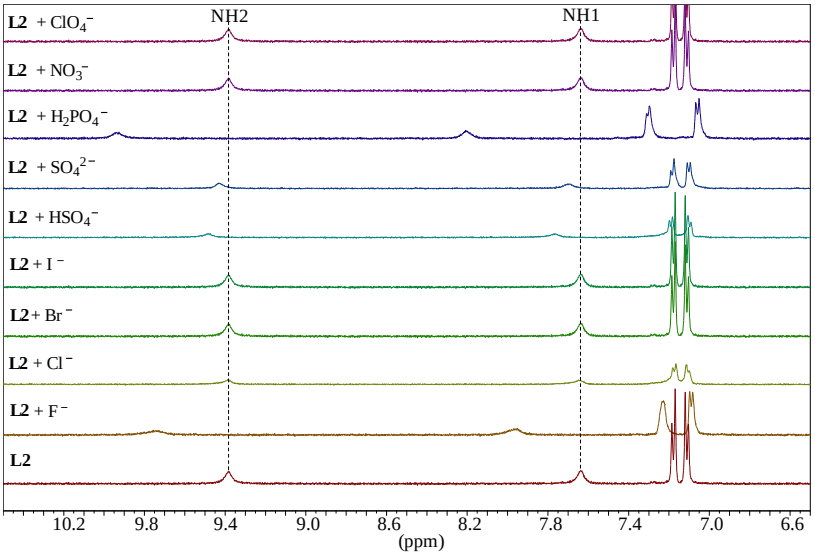


Figure 8. Partial ^{1}H NMR titration of **L2** (2 x 10^{-3} M) against 1 equiv. of various anions in DMSO-d_6. (NH2 = CSN*H*Ar, NH1 = CH_2N*H*CS).

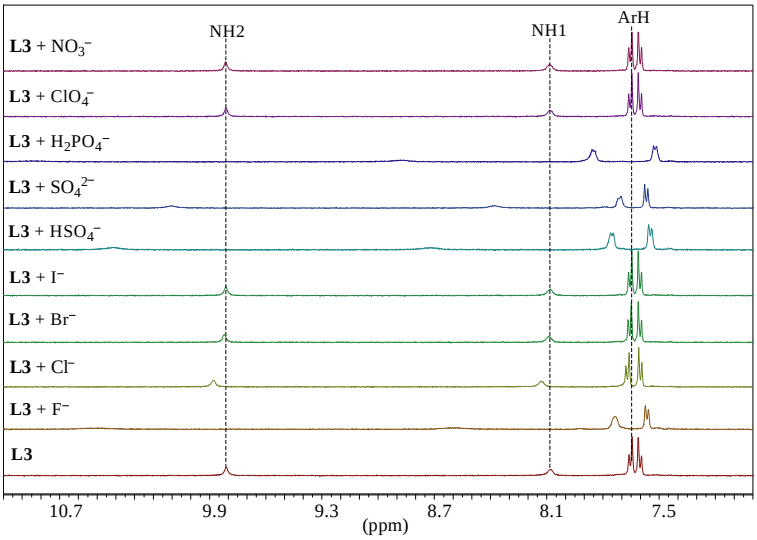


Figure 9. Partial ^{1}H NMR titration of **L3** (2 x 10^{-3} M) against 1 equiv. of various anions in DMSO-d_6. (NH2 = CSN*H*Ar, NH1 = CH_2N*H*CS).

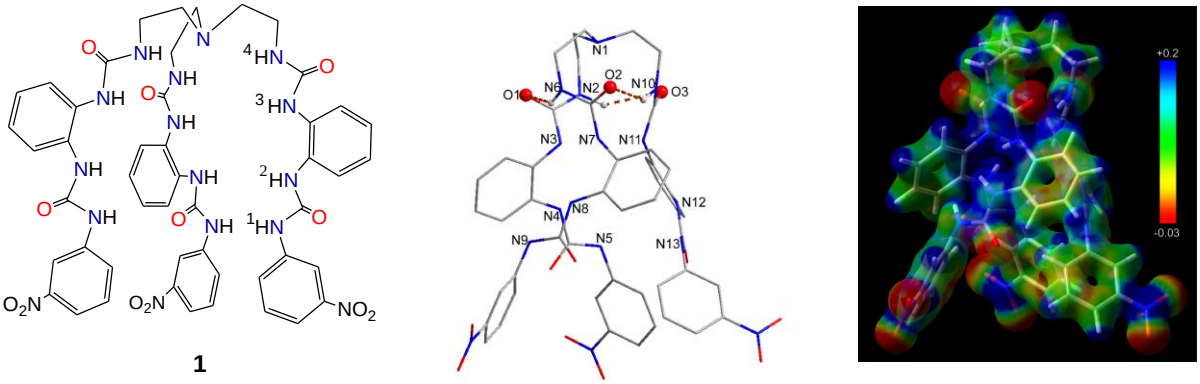
Full titrations with 10 equiv. of anions against **L1**, **L2**, and **L3** in DMSO-d_6 were performed for only F^-, Cl^-, HSO_4^-, SO_42^-, and $H_2PO_4^-$ since 1 equiv. of Br^-, I^-, ClO_4^-, and NO_3^- did not induce substantial shifts of the NH peaks upon addition to the receptors. Among the halides, **L1** and **L2** exhibited the highest binding constants for Cl^- with Log *K* (M^{-1})'s of 2.32 and 2.21 respectively. For **L3**, the highest binding was exhibited for F^- among the halides with a Log *K* (M^{-1}) of 2.96. Exceptionally, the NH peaks of **L1** and **L3** proceeded gradually against F^- via trivial shifts until disappearance of the peaks before completion of the experiment. The aromatic peaks were monitored alternatively to calculate the binding constants of the **L1** and **L3** against F^-. **L2** did not exhibit similar behavior in its titration with F^-. Among the oxoanions, the highest binding was achieved for $H_2PO_4^-$ for all of the receptors. For **L1** and **L2**, progressive shifts of NH peaks were observed and subjected to nonlinear regression analysis resulting in Log *K* (M^{-1}) of 3.14 and 3.10 respectively. For **L3**, disappearance of NH peaks was observed at 2.8 equiv. Monitoring of the one of **L3**'s aromatic peaks' progressive shifts resulted in a Log *K* (M^{-1}) of 3.62. Inductive effect of the aryl functional groups on the NH's of the thiourea moiety is accountable for the significant differences in binding constants for each of the receptors in this study. The highest binding affinities were observed for **L3** owing to the enhanced acidity of its aryl spacer group over its counterparts. **L1** and **L2** exhibited lower binding affinities than **L3** for anions correlating to the lower relative acidities of their aryl spacers groups. Similar binding affinities for F^-, Cl^-, HSO_4^-, and $H_2PO_4^-$ were observed between **L1** and **L2** are expected due to the close relative acidities of their aryl spacer moieties. The most distinguishable binding affinities for **L1**, **L2**, and **L3** were observed in the titration experiments against SO_4^{2-} with Log *K* (M^{-1}) of 2.17, 1.80, and 2.78 correlating with the relative acidities of their aromatic spacers, **L3** > **L1** > **L2**. The binding data is listed in Table 2>

Table 2. Binding Constants (*K*) from ^{1}H NMR titrations of **L1-L3**.

Receptors	Log *K* (M^{-1})					Preferred
	F^-	Cl^-	HSO_4^-	SO_4^{2-}	$H_2PO_4^-$	A^-
L1	2.16	2.32	2.18	2.17	3.14	F^-
L2	2.11	2.21	2.17	1.80	3.10	F^-
L3	2.96	2.50	2.78	2.35	3.62	F^-

3. Ditopic binding of halides by a *m*-nitrophenyl-functionalized hexaurea receptor

A tripodal-based hexaurea receptor **1** appended with *m*-nitrophenyl groups has been studied for halide binding by ^{1}H NMR, UV-Vis titrations, and high level density functional theory (DFT) calculations (**Figure 10**). As demonstrated by experimental and computational results, the receptor effectively binds a halide ion in a 1:2 binding mode showing the binding strength in the order of fluoride > chloride > bromide > iodide. The strongest affinity for fluorides is attributed to the best fit of two fluoride anions within the host's cavity. This is also supported by DFT calculations, showing that each anion is stabilized by six NH···F bonds - one at the *inner cleft* and other at the *outer cleft*.



1

a **b** **c**

Figure 10. Receptor **1**: (a) chemical structure, (b) perspective view of the optimized structure, and (c) electrostatic potential map calculated at the M06-2X/6-31G(d,p) level of theory (red = negative potential, and blue = positive potential).

NMR Studies. ^{1}H NMR studies were performed to evaluate the binding interactions of **1** for halides (F^-, Cl^-, Br^-, and I^-) as their tetrabutylammonium $[n\text{-}Bu_4N]^+$ salts in DMSO-d_6 at room temperature. The receptor exhibited four distinct NH resonances at 9.66 (H1), 8.18 (H2), 7.97 (H3) and 6.56 ppm (H4) that are consistent with its C_3 symmetric conformation. **1** was initially screened after the addition of 5 equiv. of the different halides as shown in **Figure 11**. For the addition of chloride, an appreciable downfield shift of NH resonances was observed, while the aromatic protons shifted upfield. However, the addition of fluoride to the receptor led to signal broadening of the receptor. On the other hand, a negligible change in the proton resonances was observed due to the addition of bromide or iodide to **1**.

Figure 12 shows the stacking of ^{1}H NMR titration spectra of **1** upon the incremental addition of chloride (0 to 10 equiv.), showing a progressive change of proton resonances. The change in the chemical shift of the NH resonances as a function of the chloride concentration provided the best fit for a 1:2 binding model, yielding both a 1:1 complex and a 1:2 complex. The calculated binding constants are: log K_{11} = 2.55 and log K_{12} = 3.06. In the case of fluoride, CH (aromatic) signals were used to calculate the binding constants, yielding log K_{11} = 2.06 and log K_{12} = 3.82. The overall binding constants (in log β_2) of **1** are 6.67 and 5.58 for fluoride and chloride, respectively. A cyclic hexaurea with four xanthene and two diphenyl ether units prepared by Böhmer and coworkers was found to form a 1:2 complex with chloride.We previously reported a paraxylene-based macrocyclic amine that was shown to form 1:2 complex, providing the binding constants (in log β_2) of 4.05 and 4.00 for fluoride and chloride, respectively in D_2O. However, the binding constants for bromide and iodide could not be determined by ^{1}H NMR titrations due to the negligible change in the proton resonances during titrations.

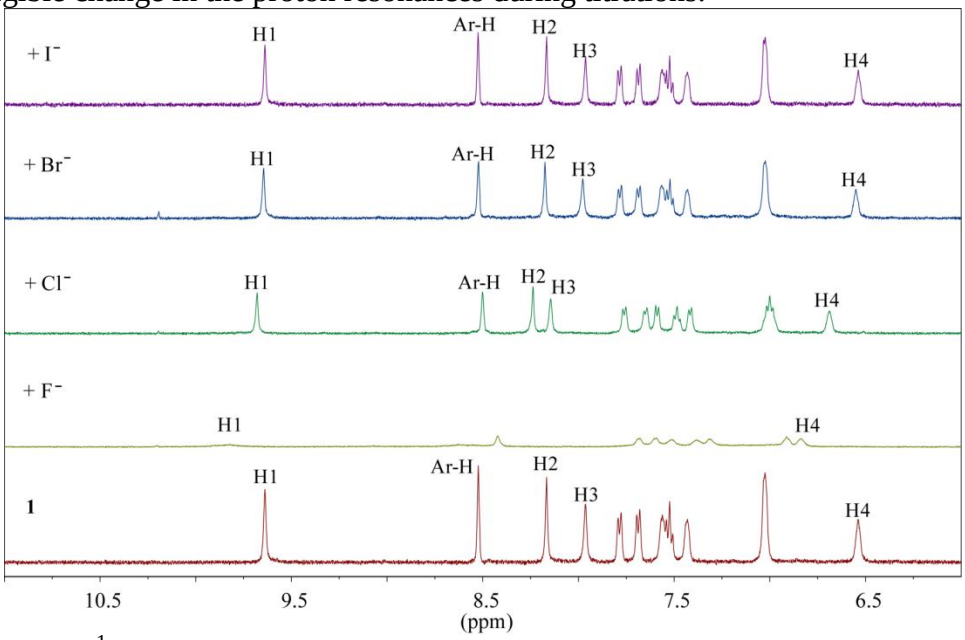


Figure 11. Partial ^{1}H NMR spectra of **1** in the presence of 5 equiv. of halides in DMSO-d_6 ($[\mathbf{1}]_0$ = 2 mM), showing changes in the NH chemical shifts in DMSO-d_6 (see, Chart 1 for the assignment of NH peaks).

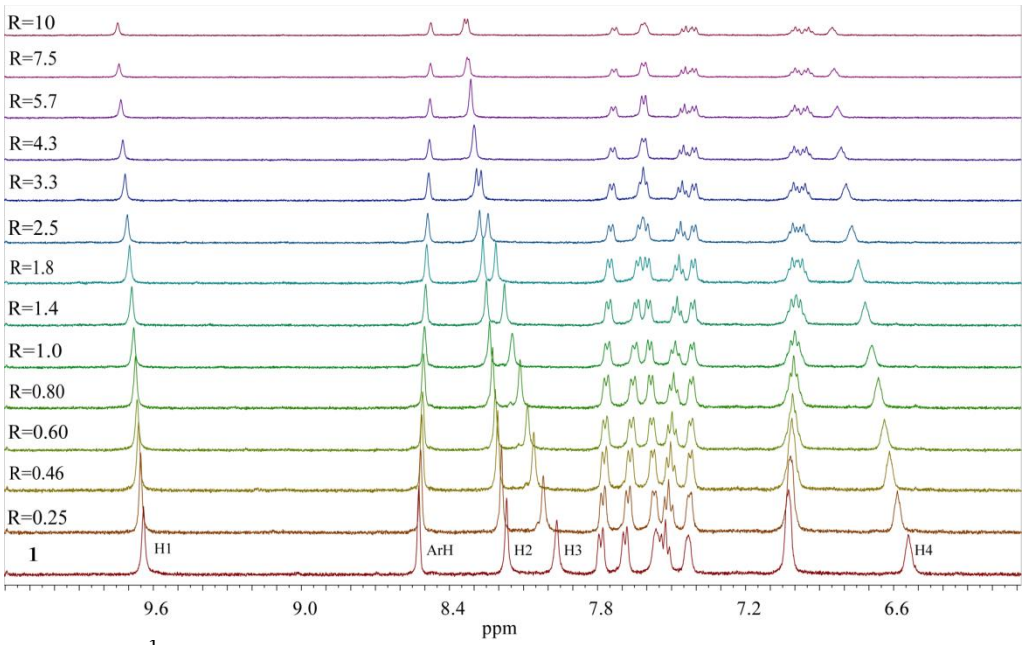


Figure 12. Partial ^{1}H NMR titration of **1** (2mM) showing changes in the NH chemical shifts with an increasing amount of Cl^{-} (20mM) in DMSO-d_6.

UV-Vis Studies: The binding interactions of the receptor were studied by UV–Vis spectroscopy in DMSO using $[n\text{-}Bu_4N]^{+}$ salts of halides. The receptor **1** containing nitrophenyl groups on the *outer cleft* showed an absorption band at λ_{max} = 351 nm. Upon the addition of a halide to **1**, the absorption was changed with respect to both the intensity and wave length (**Figure 13**). Such a change is attributed to the interaction of a halide anion with the receptor, leading to the formation of a host-guest complex.

The incremental addition of F^{-} to **1** in DMSO resulted in a gradual bathochromic (red) shift in the absorbance band (351 to 358 nm) with a gradual decrease in the absorption intensity, displaying an isosbestic point at 368 nm (Figure 4a). Whereas with other halides, the absorption intensity increased without shifting the absorption band or yielding any isosbestic point. A visible color change from light yellow to red also occurred upon the addition of fluoride to **1** (**Figure 14**), supporting the formation of the complex that is accompanied by the red shift in the absorbance band. However, the addition of other halides did not make any significant color change to the receptor. The change in the absorption intensity of **1** upon the gradual addition of a halide provide the best fit for a 1:2 binding mode. As listed in Table 3, the binding process involves the formation of both a 1:1 complex and a 1:2 complex. The association constants of **1** for 1:1 binding (in log K_{11}) are 2.11, 2.55, 2.61, and 2.92 for fluoride, chloride, bromide, and iodide, respectively. On the other hand, the association constants for 1:2 binding (in log K_{12}) are 4.66, 3.03, 2.71 and 1.12 for fluoride, chloride, bromide, and iodide, respectively. The binding trend for a 1:2 complex (fluoride > chloride > bromide > iodide) suggests that the formation of a 1:2 complex is influenced by the respective size of a halide. This is also in agreement with the results of DFT calculations. Furthermore, this binding order indicates that two larger anions in a single cavity could experience a stronger electrostatic repulsion, thereby weakening the stability of a 1:2 complex with a larger guest. In contrast, the binding trend for a 1:1 complex in the order

of iodide > bromide > chloride > fluoride, demonstrates that the 1:1 binding mode is preferred for a larger anion. The overall binding constants (in log β_2) are 6.77, 5.58, 5.32 and 4.04 for fluoride, chloride, bromide, and iodide, respectively. This suggests that the binding strength correlates with the relative basicity of halides.

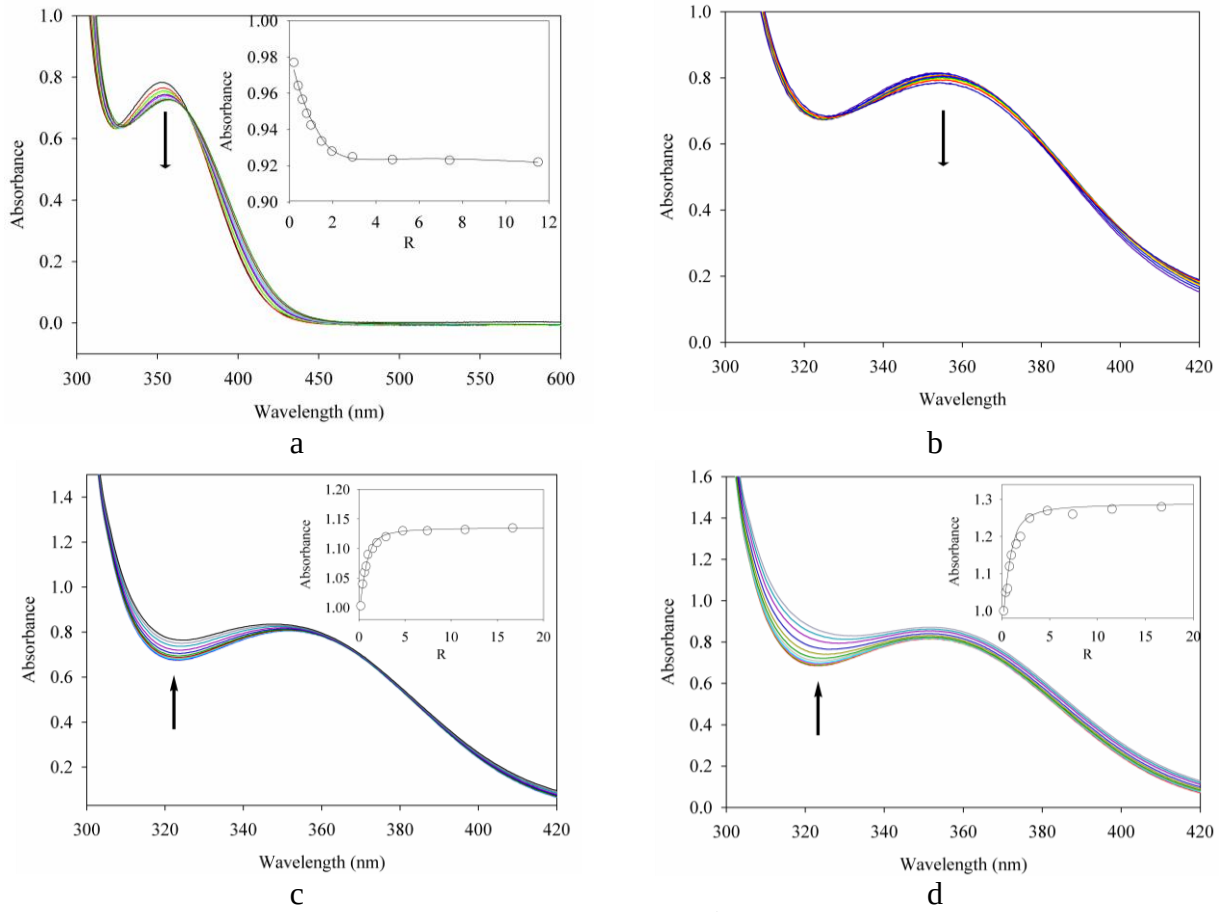


Figure 13. Changes in absorption spectra of **1** (1.5×10^{-4} M) with an increasing amount of fluoride (a), bromide (b), chloride (c), and iodide (d) in DMSO. The titration curves are shown in insets.

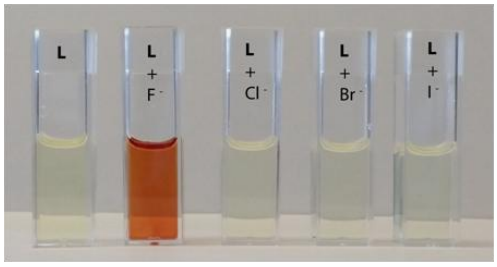


Figure 14. Colorimetric studies of **1** (2 mM) with one equivalent of different halides in DMSO, showing a color change for fluoride.

Table 1. Binding data of **1** for halides.

Anion	Log K_{11} (1:1 binding)	Log K_{12} (1:2 binding)	Log β_2 ($\beta_2 = K_1K_2$)
Fluoride	2.06 [a]	4.61 [a]	6.67 [a]
	2.11 [b]	4.66 [b]	6.77 [b]
Chloride	2.55 [a]	3.03 [a]	5.58 [a]
Bromide	2.61 [b]	2.71 [b]	5.32 [b]
Iodide	2.92 [b]	1.12 [b]	4.04 [b]

[a] Determined by ^{1}H NMR titrations in DMSO-d_6; [b] determined by UV-Vis titrations in DMSO.

Computational Studies.

In order to predict the energies involved in host-guest interactions and to understand the structural details of the complexes of **1**, we carried out theoretical calculations using ground-state density functional theory (DFT) and excited-state time-dependent density functional theory (TD-DFT). All theoretical calculations were performed using DFT method with hybrid meta-exchange correlation functional M06-2X, available in the Gaussian 09 package of programs. All the geometries were fully optimized without symmetry constraints at the M06-2X level of theory. For the complexes of fluoride, chloride and bromide, the double-ζ basis set, 6-31G(d,p) was used, while the pseudopotential basis set LANL2DZ was used for iodide complex. The Barone-Tomasi polarizable continuum model (PCM) was used to simulate the solvated environment (DMSO) of an anion. The force constants were defined analytically in the analysis of harmonic vibrational frequencies for all of the complexes. In order to compare the experimental results, we continued to optimize anion complexes by placing one halide and two halides separately within the cavity of the optimized receptor, and obtained structures of both 1:1 and 1:2 complexes for halides. The detailed hydrogen bonding interactions for 1:1 complexes ([**1**(F)]$^-$, [**1**(Cl)]$^-$, [**1**(Br)]$^-$ and [**1**(I)]$^-$) and 1:2 complexes ([**1**$(F)_2]^{2-}$, [**1**$(Cl)_2]^{2-}$, [**1**$(Br)_2]^{2-}$ and [**1**$(I)_2]^{2-}$) are provided in supporting information. The relative binding energies were determined with zero-point correction for the gas phase and the solvent-phase (DMSO) energies based on the single point calculations. Local minimum energy structures are found by ascertaining that all the harmonic frequencies are real. The calculations include both 1:1 binding (receptor with one anion) and 1:2 binding (receptor with two anions) for each halide (X^- = F^-, Cl^-, Br^- or I^-) both in gas phase and solvent phase.

As demonstrated by the optimized structure of **1** with an empty cavity (**Figure 10 b**), three identical arms (*ortho*-phenylene-bridged) linked to the *tren* backbone, lead to the receptor adopting an ideal C_3 symmetric cone shape with one *inner cleft* and one *outer cleft*. The *inner cleft* is decorated with three NH···O intra-molecular H-bonding interactions with an equidistance of NH···O = 3.14 Å, where each oxygen atom of the urea moiety is H-bonded with a single NH of an adjacent arm. All NH groups in the *inner cleft* are pointed inside the cavity, thus leading the receptor preorganized for anion binding. However, such an interaction is absent at the *outer cleft* of the receptor. The electrostatic potential surface of **1** calculated at the M06-2X/6-31G(d,p)

level of theory exhibits the most electrostatic positive potential at the center of each cleft (**Figure 10c**), making the molecule potential as a ditopic anion receptor.

1:1 complexes

The structures of 1:1 halide complexes of **1**, as obtained from the DFT calculations, are shown in Figure 15. Hydrogen-bonding parameters of the corresponding complexes are provided in Supporting Information. The structural geometries of each complex reveal that the receptor is organized to encapsulate each of halides retaining its C_3 conformation.

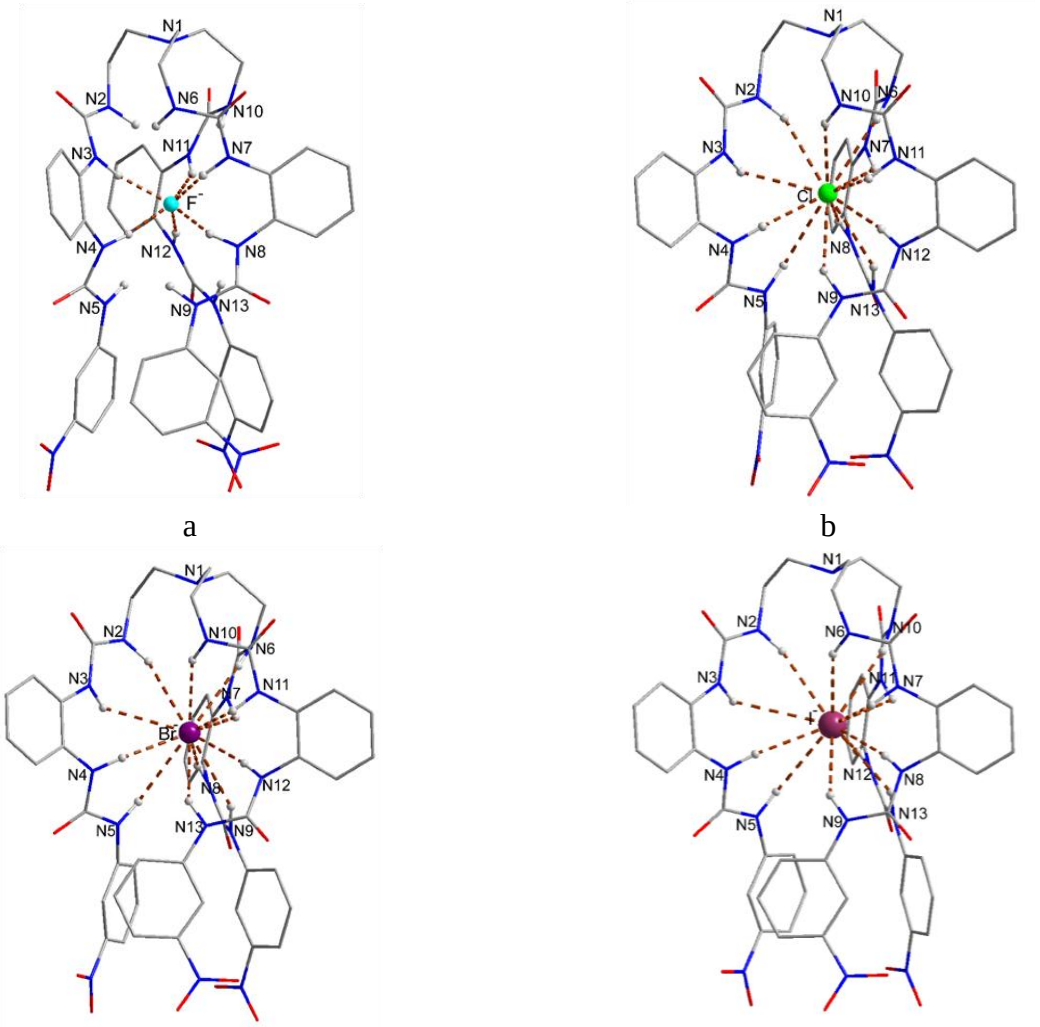


Figure 15. Perspective views of the optimized structures of 1:1 complexes: Perspective views of the optimized structures of 1:1 complexes: (a) [**1**(F)]$^-$, (b) [**1**(Cl)]$^-$, (c) [**1**(Br)]$^-$ and (d) [**1**(I)]$^-$.

With the exception of the fluoride complex, all NH binding sites in each of the three complexes (chloride, bromide and iodide complexes) are pointed towards the center forming a total of twelve H-bonds. [$d_{H\cdots Cl}$ = 2.281–2.701 Å, $d_{N\cdots Cl}$ = 3.283–3.598 Å, $d_{H\cdots Br}$ = 2.416–2.818 Å, $d_{N\cdots Br}$ = 3.413–3.669 ~~3.598~~ Å, $d_{H\cdots I}$ = 2.623–3.207 Å and $d_{N\cdots I}$ = 3.633–3.857 Å]. For the fluoride complex, the encapsulated fluoride locating at the center of the cavity is held with six H-

bonds from the surrounding NH binding sites (three from the *inner cleft* and three from the *outer cleft*) [$d_{H\cdots F}$ = 1.717–1.884 Å, $d_{N\cdots F}$ = 2.721–2.826 Å] instead of twelve H-bonds revealed for the other halide ions. Due to the smaller size of the fluoride compared to other halides, the other six NH groups (N2, N6, N10, N5, N9 and N13) linked at the far end of the *o*-xylene spacers are not involved in H-bonding interactions. In each of the halide complexes, the terminal aromatic groups are stacked to each other through CH$\cdots\pi$ interactions.

The calculated binding energies for 1:1 complexes are -168, -96, -93 and -59 kcal/mol for fluoride, chloride, bromide and iodide, respectively in gas phase. In PCM model, the corresponding binding energies are much lower as -99, -44, -16, -12 kcal/mol for fluoride, chloride, bromide and iodide, respectively, due to the included polarity included in the calculations. The relative of binding energies in the order of fluoride > chloride > bromide > iodide are in accord with their respective basicity.

1:2 complexes

The DFT-optimized structures of 1:2 halide complexes of **1** are displayed in Figure 16. In the fluoride complex, each cleft (*inner* or *outer*) is occupied by a single fluoride with six H-hydrogen bonds in an ideal C_3 symmetric conformation. The H-bonding patterns in the 1:2 complexes of chloride, bromide and iodide are different than that found in the fluoride complex. In the complexes of chloride and bromide, the *inner* halide is bound by nine hydrogen bonds with NH groups, six from the *inner cleft* and three from the *outer cleft* [$d_{H\cdots Cl}$ = 2.303–2.775 Å, $d_{N\cdots Cl}$ = 3.220–3.649 Å, $d_{H\cdots Br}$ = 2.461–2.843 Å and $d_{N\cdots Br}$ = 3.367–3.724 Å]. The distances between the halides and the tertiary nitrogen (N1) are 4.909, 4.870 and 4.135 Å in the chloride, bromide and fluoride complexes, respectively. The longer distance from N1 to the chloride or bromide, as compared to the corresponding distance observed in the fluoride complex, could be the effect of the relative anionic size and the additional three NH$\cdots$anion interactions from the *outer cleft*. On the other hand, the second halide is bound by six hydrogen bonds from three NH$\cdots$anion interactions of the *outer cleft* [$d_{H\cdots Cl}$ = 2.171–2.250 Å, $d_{N\cdots Cl}$ = 3.194–3.243 Å, $d_{H\cdots Br}$ = 2.349–2.433 Å and $d_{N\cdots Br}$ = 3.368 –3.421 Å] and three CH$\cdots$anion interactions of the terminal aromatic groups [$d_{H\cdots Cl}$ = 2.721–2.766 Å, $d_{C\cdots Cl}$ = 3.636–3.657 Å, $d_{H\cdots Br}$ = 2.795–2.908 Å and $d_{C\cdots Br}$ = 3.737–3.811 Å]. The iodide complex is found to be structurally deformed where each iodide is bound unsymmetrically. The *inner* iodide is bound by eight NH$\cdots$I bonds, while the *outer* iodide is bound with three NH$\cdots$I and two CH$\cdots$I bonds.

The binding energies for 1:2 complexes are found to be -258, -112, -113 and -76 kcal/mol for fluoride, chloride, bromide and iodide, reactively in gas phase. In the PCM model, the corresponding binding energies are -169, -59, -36, -33 kcal/mol for fluoride, chloride, bromide and iodide, respectively. The higher binding energies for 1:2 complexes than those predicted for 1:1 complexes, demonstrate that a 1:2 halide complex is stronger than a corresponding 1:1 halide complex. Further, the relative order of binding energies: fluoride > chloride > bromide > iodide is in agreement with the order of overall binding constants observed experimentally.

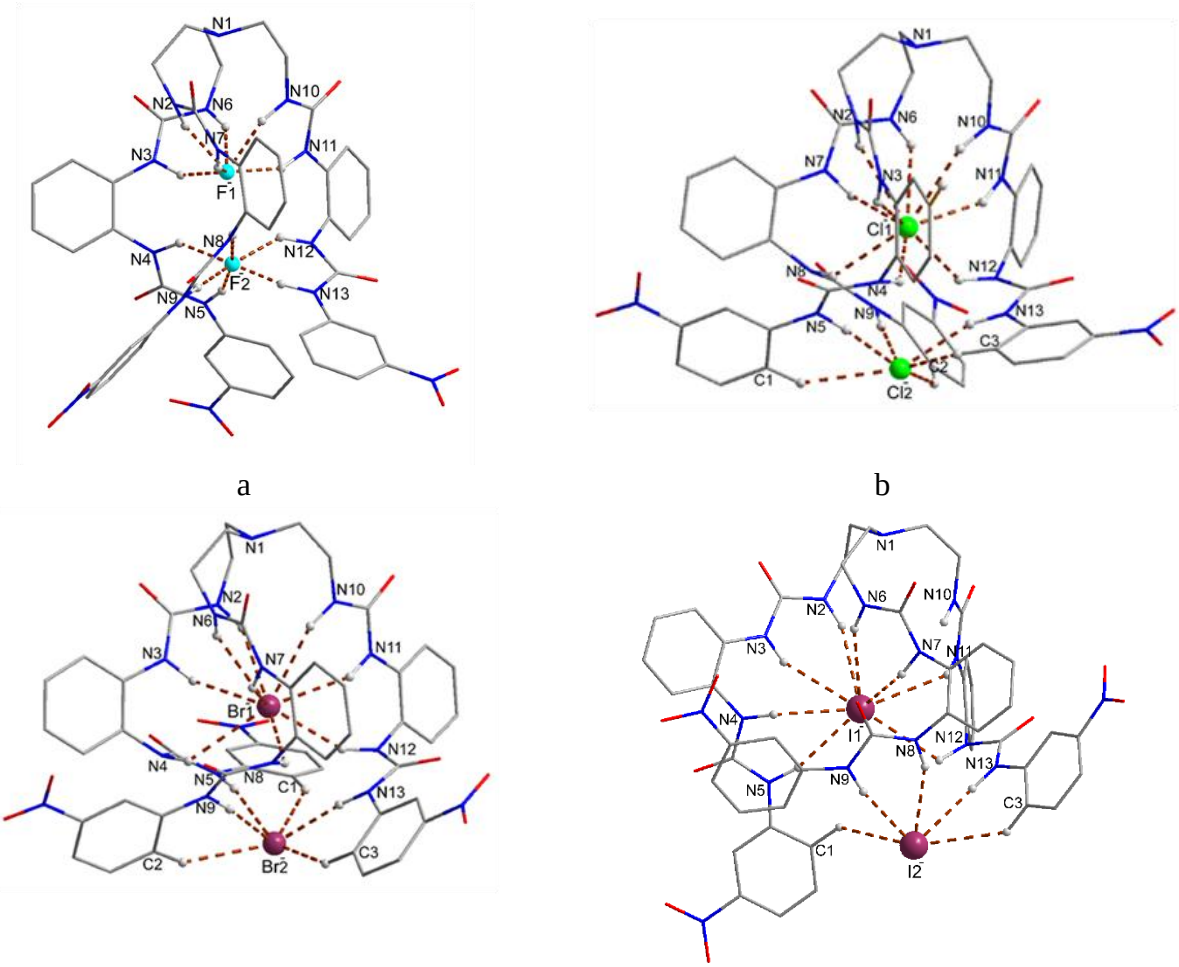


Figure 16. Perspective views of the optimized structures of 1:1 complexes: (a) $[\mathbf{1}(F_2)]^{2-}$, (b) $[\mathbf{1}(Cl_2)]^{2-}$, (c) $[\mathbf{1}(Br_2)]^{2-}$ and (d) $[\mathbf{1}(I_2)]^{2-}$.