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Radical scavenging and anti-inflammatory activities of (hetero) arylethenesulfonyl fluorides: Synthesis and structure-activity relationship (SAR) and QSAR studies

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ABSTRACT

A series of (hetero)arylethenesulfonyl fluorides (**1–58**) were synthesized and screened for their *in vitro* antioxidant (DPPH, ABTS and DMPD methods) and anti-inflammatory activities. The results revealed that compounds **4**, **15**, **16**, **24**, **25**, **26**, **38**, **39**, **40**, and **54** exhibited excellent antioxidant activity using all the three performed antioxidant methods, which were superior to the standard antioxidants ascorbic acid and gallic acid. Compounds **6–9**, **11**, **18**, **19**, **21**, **22**, **30**, **39**, **40**, **44**, **45**, **48–50**, **54**, **55** and **57** displayed promising anti-inflammatory activity, which were better than the reference drug indomethacin. Preliminary structure–activity relationship (SAR) revealed that compounds containing electron donating (−OH and $-OCH_3$) groups on the phenyl ring possessed excellent antioxidant properties while compounds containing electron-withdrawing (−Cl, $-NO_2$, −F and −Br) groups on the phenyl ring were found to be most potent anti-inflammatory agents. The presence of $-SO_2F$ group played a crucial role in increases both antioxidant and anti-inflammatory activities.

1. Introduction

Development of antioxidant agents is one of the most promising approaches searching treatments of health disorders [1]. The human bodies were exposed to free radicals, resulting in oxidative stress which imbalance oxidants, such as reactive oxygen species (ROS), and antioxidants, such as superoxide dismutase (SOD). This favours oxidant to damage protein, lipid-oxidation, and DNA which is associated with age-related cataract, age-related macular degeneration (AMD), Alzheimer's disease (AD) [2–5] atherosclerosis, cancer, neurological disorders, diabetes, ischemia/reperfusion, and aging [6–9]. To protect cells and organs against free radicals, biological systems have evolved a highly sophisticated and complex antioxidant system constitutes the body's first line of defence against free radical damage [10]. Identification of natural or synthetic potent antioxidants that have little or no pro-oxidant effects would clearly be beneficial for biological applications.

According to the World Health Organization, 90% of diseases are associated with pain. Despite growing knowledge of endogenous nociceptive and antinociceptive systems, many pain syndromes like rheumatoid arthritis and certain advanced cancers are still not adequately treated [11–13]. Currently available non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, indomethacin and naproxen, exhibit gastric toxicity. Long-term use of these drugs has been associated with gastrointestinal (GI) ulceration, bleeding and nephrotoxicity [14–16].

Sulfur(VI) Fluoride Exchange (SuFEx), is a rapidly developing new family of click chemistry transformations introduced by Professor

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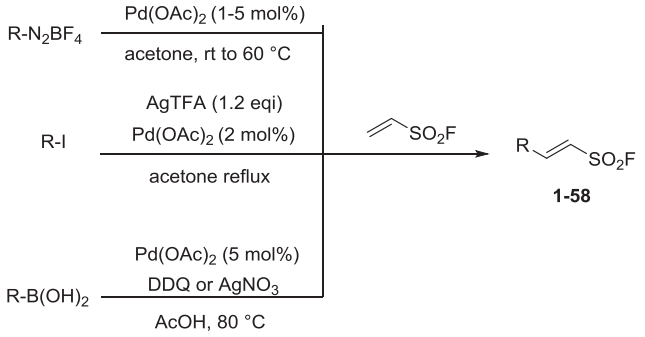


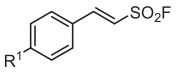
Scheme 1. The schematic representation of synthesis of (hetero)arylethenesulfonyl fluorides and 1,3-dienylsulfonyl fluorides.

Sharpless in 2014 [17]. The features of SVI-F species of strong electron withdrawing nature, stability against hydrolysis, resistance to reduction at sulfur, and crisp preference for two-electron processes over radical processes, have made S(VI)-F moieties widely applicable in chemical biology and drug discovery in a short period [18]. The practical methods for the synthesis of arylethenesulfonyl fluorides as a class of selectively addressable *bis*-electrophiles for SuFEx were developed [19]. Both the conjugated olefin moieties and the sulfonyl fluoride functionalities are reported to play significant roles in drug discovery [20]. Based on the above observations and our ongoing research in organic chemistry and medicinal chemistry [21–30], herein we report the synthesis of (hetero)arylethenesulfonyl fluoride analogues (Scheme 1) and evaluated them for their *in vitro* antioxidant and anti-inflammatory activities.

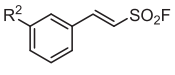
2. Results and discussion

2.1. Chemistry

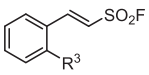
The (hetero)arylethenesulfonyl fluorides (**1–58**) were synthesized through Heck-type of coupling of ethenesulfonyl fluoride with diazonium salts, aryl iodines, or aryl boronic acids. All the derivatives were obtained in good to excellent yields. All the chemical structures were confirmed by ^{1}H, ^{13}C, ^{19}F NMR and mass spectral analysis [19c,23,24].



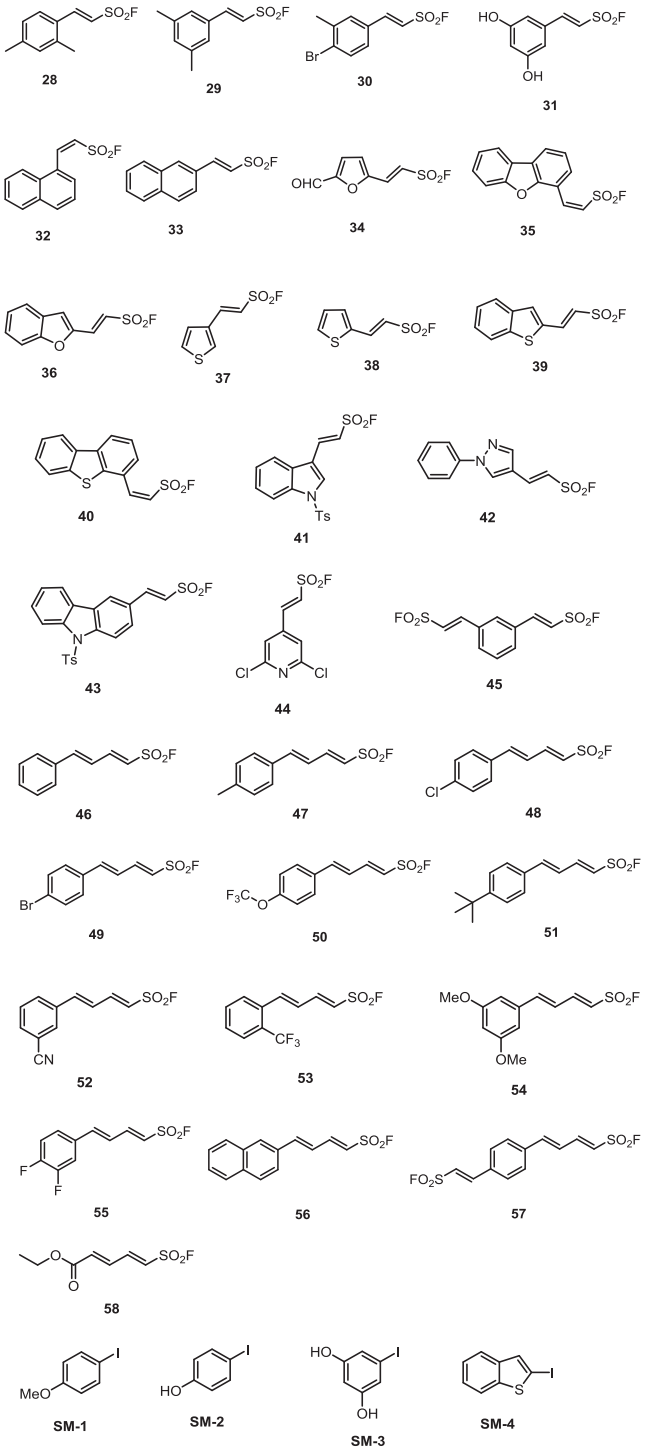
1, R^1 = H
2, **R^1 = Et**
3, R^1 = OPh
4, **R^1 = OMe**
5, R^1 = Ph
6, **R^1 = F**
7, R^1 = Cl
8, **R^1 = Br**
9, R^1 = CF_3
10, R^1 = Ac
11, R^1 = NO_2
12, R^1 = CN
13, R^1 = COOEt
14, R^1 = CHO
15, R^1 = OH



16, R^2 = OMe
17, R^2 = Me
18, R^2 = F
19, R^2 = Br
20, R^2 = I
21, R^2 = NO_2
22, R^2 = CF_3
23, R^2 = Ac
24, R^2 = OH



25, R^3 = OMe
26, R^3 = OH
27, R^3 = CHO



2.2. Biology

2.2.1. Antioxidant activities

The (hetero)arylethenesulfonyl fluorides (**1–58**) were synthesized and evaluated for their *in vitro* antioxidants activity by using (i) DPPH assay [31] which is a rapid and convenient technique for screening the antioxidant activities of the compounds, (ii) ABTS cation radical assay [32] which is a conventional and excellent model for assessing the antioxidant activities of hydrogen donating and chain breaking antioxidants, and (iii) DMPD cation radical assay [33] which is similar to the DPPH radical scavenging assay. The values of IC_{50}, the effective

Table 1
Antioxidant and anti-inflammatory activity of synthesized compounds (**1–58**).

Entry	Antioxidant activity[a] (IC_{50} μg/mL)			Anti-inflammatory activity[a] (IC_{50} μg/mL)
	DPPH	ABTS	DMPD	
1	96.14 ± 2.10	86.09 ± 3.12	–	85.42 ± 1.64
2	68.33 ± 1.33	62.10 ± 2.72	72.08 ± 3.10	80.40 ± 2.61
3	64.19 ± 2.07	58.13 ± 2.76	58.16 ± 1.67	70.20 ± 1.09
4	32.30 ± 1.08	34.24 ± 1.37	30.22 ± 1.07	90.45 ± 1.26
5	64.48 ± 2.35	78.16 ± 3.66	56.77 ± 2.93	68.54 ± 1.30
6	76.88 ± 2.07	78.08 ± 2.84	80.42 ± 3.17	28.55 ± 1.61
7	82.36 ± 3.07	90.50 ± 2.62	88.86 ± 1.54	32.08 ± 1.20
8	80.10 ± 2.84	70.64 ± 1.04	76.27 ± 2.03	30.66 ± 1.06
9	86.32 ± 2.18	> 100	> 100	40.77 ± 2.07
10	> 100	> 100	> 100	90.39 ± 3.11
11	76.24 ± 2.45	80.62 ± 3.09	88.88 ± 2.19	34.46 ± 1.69
12	84.78 ± 3.91	88.52 ± 2.61	90.44 ± 2.33	60.61 ± 1.24
13	72.42 ± 2.55	80.64 ± 1.62	82.20 ± 1.60	78.18 ± 2.69
14	90.18 ± 2.15	72.12 ± 1.55	76.44 ± 2.62	80.31 ± 2.22
15	28.10 ± 1.06	32.22 ± 1.72	30.17 ± 1.08	78.46 ± 2.64
16	38.20 ± 1.91	36.08 ± 1.45	36.19 ± 1.07	82.17 ± 2.30
17	58.28 ± 1.30	54.30 ± 1.58	58.34 ± 1.01	64.22 ± 1.78
18	88.54 ± 2.07	82.35 ± 3.11	82.63 ± 0.41	30.24 ± 1.08
19	82.45 ± 1.09	80.33 ± 1.22	78.42 ± 1.61	34.12 ± 1.18
20	> 100	> 100	> 100	55.33 ± 2.06
21	84.17 ± 3.08	86.68 ± 2.47	82.90 ± 1.68	36.76 ± 1.84
22	90.87 ± 3.17	> 100	> 100	40.13 ± 2.01
23	82.88 ± 2.09	72.74 ± 2.44	86.68 ± 2.61	76.44 ± 2.41
24	36.32 ± 1.64	34.17 ± 1.62	34.81 ± 1.51	78.39 ± 2.60
25	32.22 ± 1.06	28.24 ± 1.12	34.84 ± 1.88	80.55 ± 2.71
26	40.86 ± 1.66	36.47 ± 1.41	32.30 ± 1.08	78.96 ± 2.45
27	78.85 ± 2.18	68.68 ± 1.44	68.47 ± 1.74	80.32 ± 1.54
28	48.31 ± 1.54	46.42 ± 1.84	46.31 ± 1.57	56.66 ± 1.30
29	52.24 ± 1.55	42.11 ± 1.08	44.33 ± 2.68	60.49 ± 2.07
30	64.64 ± 2.08	74.99 ± 1.06	62.45 ± 1.44	32.66 ± 1.54
31	18.77 ± 1.02	16.48 ± 1.12	16.04 ± 1.20	78.22 ± 2.61
32	58.07 ± 2.18	64.31 ± 2.07	60.48 ± 2.22	60.30 ± 2.17
33	60.44 ± 2.14	70.32 ± 2.44	68.10 ± 1.56	68.09 ± 1.57
34	68.33 ± 1.22	72.09 ± 2.41	72.44 ± 1.22	70.14 ± 2.40
35	46.32 ± 2.11	48.34 ± 1.64	46.04 ± 1.44	60.61 ± 2.11
36	50.55 ± 1.22	44.16 ± 1.54	48.47 ± 1.30	52.52 ± 1.44
37	52.12 ± 1.30	60.14 ± 2.22	58.22 ± 2.21	62.10 ± 2.10
38	42.11 ± 1.66	46.55 ± 2.30	42.40 ± 1.10	52.14 ± 2.01
39	32.46 ± 1.30	36.31 ± 1.10	34.49 ± 1.14	42.10 ± 1.10
40	32.10 ± 1.20	36.89 ± 2.46	36.95 ± 2.28	40.96 ± 2.22
41	52.66 ± 2.42	56.45 ± 1.67	58.87 ± 1.64	60.52 ± 1.44
42	54.16 ± 1.97	56.44 ± 2.87	52.12 ± 2.44	58.30 ± 2.47
43	48.12 ± 2.33	52.40 ± 1.10	50.33 ± 1.18	60.18 ± 1.64
44	64.39 ± 2.24	74.88 ± 2.10	66.93 ± 1.01	18.77 ± 1.10
45	66.72 ± 1.68	68.82 ± 1.20	68.24 ± 2.60	50.36 ± 1.30
46	54.64 ± 2.51	64.60 ± 1.40	64.48 ± 1.87	60.43 ± 1.20
47	50.24 ± 1.11	54.63 ± 2.22	56.40 ± 1.78	58.11 ± 2.71
48	60.11 ± 2.42	64.49 ± 1.48	60.10 ± 2.20	38.08 ± 2.10
49	56.14 ± 1.98	54.12 ± 1.32	48.48 ± 1.10	36.10 ± 1.10
50	62.21 ± 1.30	68.64 ± 2.64	66.44 ± 1.74	46.84 ± 1.46
51	64.43 ± 2.87	62.11 ± 2.66	72.42 ± 2.44	74.20 ± 2.84
52	68.46 ± 1.36	68.76 ± 2.66	74.44 ± 1.42	42.12 ± 1.10
53	70.07 ± 2.08	64.09 ± 1.30	76.40 ± 1.14	40.06 ± 1.72
54	20.08 ± 1.01	26.32 ± 1.10	30.77 ± 1.16	60.36 ± 2.11
55	60.31 ± 1.30	58.70 ± 2.30	62.73 ± 2.11	16.06 ± 1.09
56	52.48 ± 1.20	48.18 ± 1.64	56.14 ± 1.18	60.10 ± 1.33
57	48.44 ± 1.66	44.12 ± 2.31	60.48 ± 1.30	42.45 ± 1.89
58	> 100	> 100	> 100	> 100
SM-1	84.11 ± 2.30	90.45 ± 1.32	> 100	N.D
SM-2	82.13 ± 1.33	90.18 ± 1.10	84.45 ± 1.30	N.D
SM-3	78.21 ± 2.55	80.24 ± 1.30	76.71 ± 2.11	N.D
SM-4	84.76 ± 2.30	96.83 ± 3.49	82.07 ± 2.33	N.D
AA	44.19 ± 1.46	42.22 ± 1.08	44.48 ± 1.10	———
GA	46.18 ± 1.03	48.10 ± 1.40	42.13 ± 1.10	———
IM	———	———	———	44.44 ± 1.06

[a] Values are mean of three determinations, the ranges of which are < 5% of the mean in all cases. AA = Ascorbic acid; GA = Gallic acid; IM = Indomethacin.

concentration at which 50% of the radicals were scavenged, were calculated to evaluate the antioxidant activities. A lower IC_{50} value indicated greater antioxidant activity. IC_{50} values of lower than 10 mg/mL usually implied effective activities in antioxidant properties [34]. The IC_{50} values of gallic acid (GA) and ascorbic acid (AA) were also determined for comparison. The obtained results were tabulated in Table 1.

The obtained results confirmed the existence of a good structure-activity relationship for all compounds in different methods. As shown, the results of a single assay can only give an idea on potential of tested compounds. The parent compounds (**SM-1**, **SM-2**, **SM-3** and **SM-4**) were very weak radical scavengers and after conversion of iodide to sulfonyl fluorides, the antioxidant activity is significantly improved. For example, using DPPH method, the IC_{50} value of parent compound (**SM 1**) was 84 μg/mL and the after conversions of iodide to sulfonyl fluoride (**4**) the IC_{50} value was decreases from 84 to 32 μg/mL, which was about 3 times more potent than **SM-1**. However, the presence of $–SO_2F$ group has a remarkable influence on the radical scavenging ability of the screened compounds. Among them, compounds **4**, **15**, **16**, **24**, **25**, **26**, **38**, **39**, **40**, and **54** showed good radical scavenging activities with IC_{50} values 32.30 ± 1.08, 28.10 ± 1.06, 38.20 ± 1.91, 36.32 ± 1.64, 32.22 ± 1.06, 40.86 ± 1.66, 42.11 ± 1.66, 32.46 ± 1.30, 32.10 ± 1.20 and 20.08 ± 1.01 μg/mL respectively in DPPH assay better than the standards AA (IC_{50} = 44.19 ± 1.46 μg/mL) and GA (IC_{50} = 46.18 ± 1.03 μg/mL). In $ABTS^+$ radical scavenging assay, the compounds **4**, **15**, **16**, **24**, **25**, **26**, **29**, **38**, **39**, **40**, and **54** showed potent antioxidant activity with IC_{50} values 34.24 ± 1.37, 32.22 ± 1.72, 36.08 ± 1.45, 34.17 ± 1.62, 28.24 ± 1.12, 36.47 ± 1.41, 42.11 ± 1.08, 46.55 ± 2.30, 36.31 ± 1.10, 36.89 ± 2.46 and 26.32 ± 1.10 μg/mL respectively which were better than the commercial standards AA (IC_{50} = 42.22 ± 1.08 μg/mL) and GA (IC_{50} = 48.10 ± 1.40 μg/mL). The compounds **4**, **15**, **16**, **24**, **25**, **26**, **38**, **39**, **40**, and **54** also exhibited good antioxidant activity with IC_{50} values 30.22 ± 1.07, 30.17 ± 1.08, 36.19 ± 1.07, 34.81 ± 1.51, 34.84 ± 1.88, 32.30 ± 1.08, 42.40 ± 1.10, 34.49 ± 1.14, 36.95 ± 2.28 and 30.77 ± 1.16 μg/mL respectively which were better than the standards AA (IC_{50} = 44.48 ± 1.10 μg/mL) and GA (IC_{50} = 42.13 ± 1.10 μg/mL) in DMPD assay. In all the three assays performed, the compounds **4**, **15**, **16**, **24**, **25**, **26**, **38**, **39**, **40**, and **54** showed good antioxidant activities with IC_{50} values were lower than the standards.

2.2.2. Anti-inflammatory activity

Inflammation is a response of immune system that activates many enzymatic and cellular processes to protect the body from all kinds of trauma. To address this, all the synthesized compounds were evaluated for their anti-inflammatory activity using *in vitro* human erythrocytes model [35]. A significant number of compounds have been identified and showed excellent to moderate inhibitory activity compared to standard drug indomethacin. IC_{50} was determined for the compounds showing more than 50% inhibition concentration (Table 1). The compounds **6**, **7**, **8**, **9**, **11**, **18**, **19**, **21**, **22**, **30**, **39**, **40**, **44**, **45**, **48**, **49**, **50**, **52**, **53**, **55** and **57** showed excellent activity with IC_{50} values lower than the standard indomethacin (IC_{50} = 44.44 ± 1.06 μg/mL). Among them, compounds **44** and **55** showed excellent anti-inflammatory activity with IC_{50} values of 18.77 ± 1.10 and 16.06 ± 1.09 μg/mL respectively, these potent molecules (**44** and **55**) were selected for their further *in vivo* anti-inflammatory studies. The electron-withdrawing groups present on the aromatic rings, were found to be the most favorable for anti-inflammatory activities [26] and the presence of more than two electron-withdrawing groups (**44** and **55**) on the phenyl ring showed superior anti-inflammatory activity, which are better than those molecules contain a single electron-withdrawing group on the aromatic rings, **6–9**, **11** and **18–22**.

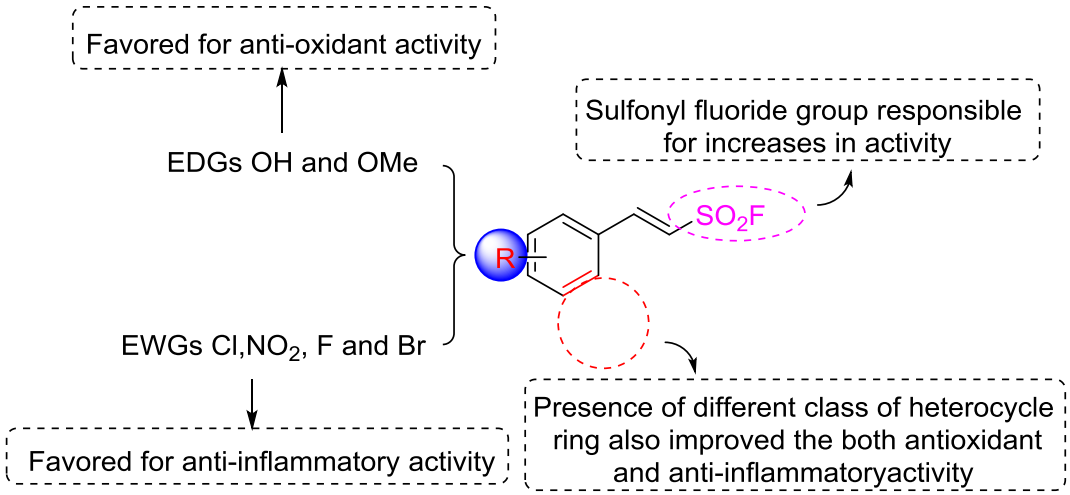


Fig. 1. Represents the SAR of antioxidant and anti-inflammatory activities of synthesized compounds.

2.2.3. Structure-activity relationship

The 58 target compounds were chemically and biologically diverse. Herein, their SAR against antioxidant and anti-inflammatory activities were summarized in Fig. 1. Based on the above observation, compounds bearing electron-donating (−OH and $-OCH_3$) groups on the phenyl ring (**4**, **15**, **16**, **24**, **25**, **26**, **38**, **39**, **40**, and **54)** were found to be good antioxidants. The conversion of iodide (**SM-1**, **SM-2**, **SM-3** and **SM-4**) group to ethenylsulfonyl fluorides ($-SO_2F$) group (**4**, **15**, **31** and **39**) significantly improved the antioxidant properties, which were about 3–4 times more potent than the corresponding starting materials (**SM-1-SM-4)**. This type of analogues may be preliminarily proved that the antioxidant activity depends on $-SO_2F$ and electron-donating groups. The presence of electron-donating methoxy (**4**) and hydroxyl (**15**) groups in *para*-position on the phenyl ring showed highest antioxidant activity compared to the compounds with electron-donating substitutions at *ortho* and *meta*-positions (**16**, **24**, **25** and **26**). The presence of methoxy group at *p*-position of aromatic ring will increase the electron density of carbon atoms in the ring [36]. Increase the number of electron-donating −OH and −OMe (**31** and **54**) groups on the phenyl ring, antioxidant activities were also significantly improved, which was revealed by comparing bist-substituted −OMe and −OH (**31** and **54**) with the mono-substituted −OMe and −OH (**4** and **15**) groups on the phenyl ring [26,37]. Moreover, different class of analogues such as thiophene, benzothiophene, furan, benzofuran and other heterocyclic derivatives were tested for their antioxidant activity. Among them, thiophene (**38**) and benzothiophene (**39**) derivatives showed potent antioxidant properties with IC_{50} values between 32.46 ± 1.30–46.55 ± 2.30 μg/mL respectively, using all the three performed antioxidant methods. The presence of electron-withdrawing (−Cl, −F, −Br and $-NO_2$) groups (**6–9**, **11**, **18–22**, **48**, **50**, **53** and **55**) on the phenyl ring exhibited the least antioxidants activity. Herein, their SAR against anti-inflammatory activity was summarized. The present results indicate that the anti-inflammatory activity depends on the nature of the substituents present on the phenyl ring. The presence of electron-withdrawing (−Cl, −F, −Br, $-NO_2$ and $-CF_3$) groups on the any position of phenyl ring showed promising anti-inflammatory activity [26,37]. Among them, electron-withdrawing group presents in *para*-position on the phenyl ring (**6–9** and **11**) showed an excellent anti-inflammatory activity compared to those possessing *meta*-position substituents (**18–22**). The presence of electron-donating groups (−OH and $-OCH_3$) on the phenyl ring showed least anti-inflammatory activity. Compound **55** (IC_{50} = 16.06 ± 1.09 μg/mL) was found to be most potent anti-inflammatory agent, may be due to presence of two fluorine atoms on the phenyl ring, which is expected as it is well known that fluorine atom usually plays a very important role in medicinal chemistry due to its versatility [38,39].

2.2.4. 3D-QSAR studies

2.2.4.1. Pharmacophore model generation and validation. PHASE is a versatile module for pharmacophore perception, structural alignment, activity prediction, and 3D database creation and searching. Pharmacophore from all the conformations of the ligand in the active sites were examined, and the pharmacophores that contain identical sets of features with very similar spatial arrangements were grouped together. Common pharmacophores were identified using a tree-based partitioning technique that groups of similar pharmacophores. After applying default feature definitions to each ligand, common pharmacophores containing five sites were generated using a terminal box size of 1 Å where all the active molecules match [22].

2.2.4.2. 3D-QSAR visualization. For 3D-QSAR studies, the total set of **58** (hetero)arylethenesulfonyl fluorides were used as training set for generation of 3D-QSAR models and a 2-standards were used as test-set for validation of the developed model. For QSAR development, models of the pharmacophore features of the training set molecules were placed into a regular grid of cubes where each cube allotted zero for the different types of pharmacophore features in the training set that occupy the cube (1 Å). This representation gives rise to binary-valued occupation patterns that can be used as independent variables to create 3D-QSAR models with partial least-squares (PLS) factors. Statistics for the correlation of the predicted activity with the actual activity were collated for the hypothesis. Atom-based QSAR models were generated for the hypothesis using the training set and contained one to five PLS factors, and the models were validated by predicting the activity of the test set of ligands.

2.2.4.3. Discussion. PHASE utilizes fine-grained conformational sampling for given a set of **58** (hetero)arylethenesulfonyl fluorides with an affinity for a target. PHASE utilizes scoring techniques which identify a common pharmacophore hypothesis that suggests the relative manner in which the molecules are likely to bind to the receptor, based on standard and conveys characteristics of the three-dimensional chemical structures that are reported to be very essential for binding. As 58 (hetero) arylethenesulfonyl fluorides are relatively small number of rotatable bonds and some common structural framework, an atom-based model was chosen. Therefore, we developed an atom-based QSAR model using training set compounds, and the model was validated by predicting the activity of the test set of standards. The best pharmacophore model resulted for antioxidant (Fig. 2**A**) and anti-inflammatory (Fig. 2**B**) are in AADRR.76 (R^2 = 0.722) and AADRR.87

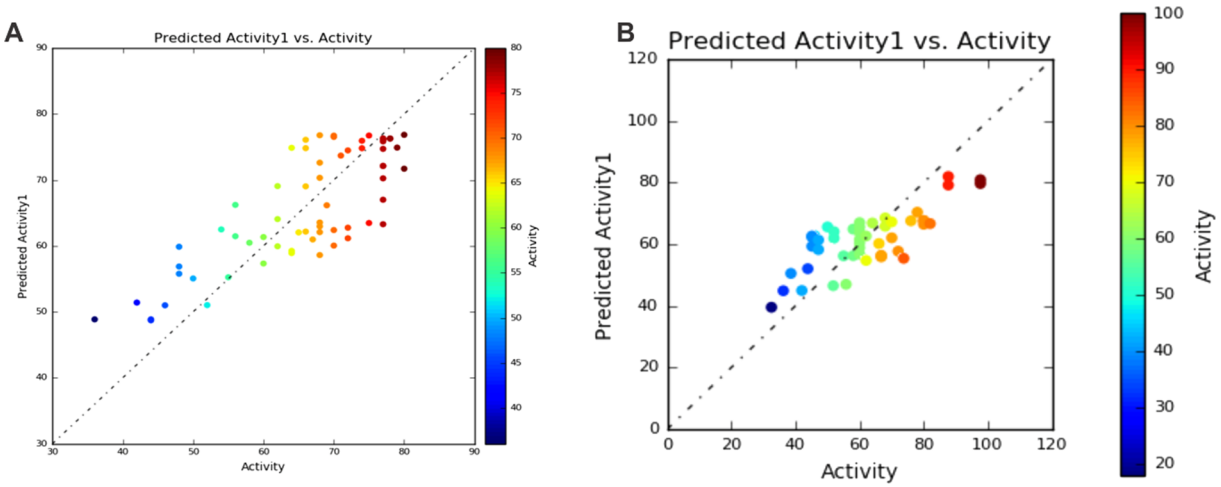


Fig. 2. Plot of observed activity versus predicted activity of tested ligands **1–58** for 3D-QSAR model generated using CPHs: AAAAR.30.

(R^2 = 0.792) respectively, with goodness of the model was validated by Q^2 = 0.69 for antioxidant and for anti-inflammatory Q^2 = 0.78 the test set.

3. Conclusion

In the present work, we synthesized a series of (hetero)arylethenesulfonyl fluorides in good yields and screened for their *in vitro* antioxidant and anti-inflammatory agents. Screening results indicated that some compounds showed excellent antioxidant and anti-inflammatory activities. Among them, compounds **4**, **15**, **16**, **24**, **25**, **26**, **38**, **39**, **40**, and **54** showed excellent antioxidant activity in all the three performed antioxidant methods, which was superior to the standard antioxidants ascorbic acid and gallic acid. Compounds **6–9**, **11**, **18**, **19**, **21**, **22**, **30**, **39**, **40**, **44**, **45**, **48–50**, **54**, **55** and **57** displayed promising anti-inflammatory activity, which was better than the reference drug indomethacin. Further, SAR study showed that the presence of -SO_2F, electrons-donating (−OH and −OCH_3) group and electron-withdrawing (−Cl, −NO_2, −F, and −Br) on the phenyl ring played an important role in both antioxidant and anti-inflammatory activity.

4. Materials and methods

4.1. Chemistry

All reactions were carried out under an air atmosphere. Unless otherwise specified, NMR spectra were recorded in $CDCl_3$ on a 500 (for ^{1}H), 471 (for ^{19}F), or 126 MHz (for ^{13}C) spectrometer. All chemical shifts are reported in ppm relative to TMS (^{1}H NMR, 0 ppm) as an internal standard. The coupling constants are reported in Hertz (Hz). The HPLC experiments were carried out on a Waters e2695 instrument (column: J&K, RP-C18, 5 µm, 4.6 × 150 mm), and the yields of the products were determined by using the corresponding pure compounds as the external standards. Melting points are reported uncorrected. MS experiments were performed on a TOF-Q ESI or CI/EI instrument. Reagents used in the reactions were all purchased from commercial sources and used without further purification.

4.1.1. Synthesis

4.1.1.1. Method 1

4.1.1.1.1. A typical procedure for the synthesis of β-(hetero) arylethenesulfonyl fluorides from benzenediazonium tetrafluoroborate [23]. Ethenesulfonyl fluoride (1.10 g, 10.0 mmol), and $Pd(OAc)_2$ (112 mg, 0.500 mmol) were added to a solution of benzenediazonium tetrafluoroborate (2.11 g, 11.0 mmol) in 40 mL acetone (more acetone should be added if the diazonium salt is not completely dissolved) at 25 °C. The resulting mixture was stirred for 5 h at room temperature before concentrated under reduced pressure. The crude was purified by flash column chromatography with 1–5% EtOAc/Hexanes and further recrystallization from hexanes and ethyl ether to yield the corresponding pure product.

4.1.1.2. Method 2

4.1.1.2.1. Procedures for the fluorosulfonylvinylation of (Hetero)Aryl iodides [24]. An oven-dried reaction tube (50 mL) was charged with AgTFA (2.4 mmol, 1.2 equiv), $Pd(OAc)_2$ (9 mg, 2 mol%), and acetone (5 mL), (hetero)aryl iodide (2 mmol) and ethenesulfonyl fluoride (440 mg, 4.0 mmol, 2 equiv) were added. The resulting mixture was refluxed at 60 °C. When aryl iodide had been consumed (6–24 h), the crude was purified by column chromatography on silica gel to obtained corresponding products.

4.1.1.3. Method 3

4.1.1.3.1. General procedures for synthesis of β-(hetero)arylethenesulfonyl fluorides from arylboronic acids [19c]. To an oven-dried reaction flask (150 mL) charged with AcOH (50 mL), arylboronic acid (10 mmol), 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ, 15.0 mmol, 1.5 equiv), $Pd(OAc)_2$ (112 mg, 5 mol%), and ethenesulfonyl fluoride (6.60 g, 60.0 mmol, 6.0 equiv) were added successively. The flask was equipped with a condenser apparatus open to the atmosphere, and the resulting mixture was allowed to react at 80 °C for 6–12 h (monitored by TLC) before concentrating under vacuum. The crude product was purified by silica gel chromatography by gradient elution with 5–20% EtOAc/Petroleum ether to obtained pure products.

4.2. Biology study

4.2.1. DPPH (1,1-diphenyl-2-picryl-hydrazyl) assay

The radical scavenging activities against DPPH free radicals of synthesized compounds were determined according to the reported method [31]. Briefly, 50 µL of test compounds was mixed at different concentrations (20, 40, 60, 80 and 100 µg/mL) with 1 mL of 0.1 mM DPPH in methanol solution and 450 µL of 50 mM Tris HCl buffer (pH 7.4). Methanol (50 µL) only was used as the experimental control. After 30 min of incubation at room temperature, the reduction in the number of DPPH free radicals was measured by reading the absorbance at 517 nm. AA and GA were used as standards similar to test concentrations. Percent inhibition was calculated from the following equation:

$$\%\text{Inhibition} = \left[\frac{\text{Absorbance of control} - \text{Absorbance of test sample}}{\text{Absorbance of control}}\right] \times 100$$

4.2.2. ABTS (2,2-azinobis-(3-ethylbenzothiazoline-6-sufonic acid) assay

The ability of the test sample to scavenge $ABTS^{\cdot+}$ radical cation was determined according to the literature method [32] with slight modifications. The $ABTS^{\cdot+}$ radical cation was pregenerated by mixing 7 mM $ABTS^{\cdot+}$ stock solution with 2.45 mM potassium persulfate (final concentration) and incubating for 12–16 h in the dark at room temperature until the reaction was complete and the absorbance was stable. The absorbance of the $ABTS^{\cdot+}$ solution was equilibrated to 0.70 (± 0.02) by diluting with distilled water at room temperature, then 2 mL was mixed with different concentration of the test sample (20, 40, 60, 80, and 100 μg/mL) and the absorbance was measured at 734 nm after 6 min. The scavenging capability of $ABTS^{\cdot+}$ radical was calculated using the following equation:

$$ABTS.^{+}\ \text{scavengingeffect}(\%) = [(A_c - A_s)/A_c]x100$$

where, Ac is the initial concentration of the ABTS. + and As is the absorbance of the remaining concentration of ABTS. + in the presence of compounds.

4.2.3. DMPD (N, N-dimethyl-p-phenylenediamine) assay

The DMPD radical scavenging ability of synthesized compounds was determined by the method [33] with slight modifications. This assay is based on the capacity of the extract to inhibit $DMPD^{\cdot+}$ cation radical formation. Briefly, 105 mg of DMPD was dissolved in 5 mL of distilled water. Then, 1 mL of this solution was added to 100 mL of 0.1 M acetate buffer (pH 5.3). $DMPD^{\cdot+}$ was produced by adding 0.3 mL ferric chloride (0.05 M) to this solution. Different concentrations of standard antioxidants or synthesized compounds (20, 40, 60, 80 and 100 μg/mL) were added, and the total volume was adjusted to 1 mL with distilled water. One milliliter of the $DMPD^{\cdot+}$ solution was directly added to the reaction mixture. The reaction mixtures were incubated in the dark for 15 min. The absorbance was measured at 505 nm.

$$\%\text{Inhibition} = \left[\frac{\text{Absorbance of control} - \text{Absorbance of test sample}}{\text{Absorbance of control}}\right] \times 100$$

4.3. Anti-inflammatory activity

4.3.1. Human erythrocyte suspension

The human blood was purchased from public hospital, Mysore, India and collected in heparinized vacutainer. The collected healthy human blood was washed with 0.9% saline and centrifuged for 10 min at 3000 rpm. The packed cells were washed with 0.9% saline and 40% v/v suspension was made by isotonic phosphate buffer of 154 mM NaCl in 10 mM Sodium Phosphate Buffer at pH 7.4 and used as stock erythrocyte or RBC suspension.

4.3.2. Hypotonic solution-induced haemolysis

The activity of the synthesized compounds was tested according to the reported method [35]. The tested sample 0.5 mL consisted of stock erythrocyte (RBC) suspension. 5 mL of hypotonic solution (50 mM NaCl in 10 mM Sodium Phosphate buffered saline at pH 7.4) and different concentrations of sample (20, 40, 60, 80 and 100 μg/mL) was prepared. The blank control consisted of 0.5 mL RBC suspension mixed and 5 mL hypotonic buffered solution alone. The mixtures were incubated for 10 min at room temperature, centrifuged for 10 min at 3000 rpm and supernatant was measured by spectrophotometrically at 540 nm. The % inhibition of hemolysis was calculated according to the following formula.

$$\%\text{Inhibition of heamolysis} = \left[\frac{A_1 - A_2}{A_1}\right] \times 100$$

where:

A_1 = Absorbance of hypotonic buffered solution alone.
A_2 = Absorbance of test/standard sample in hypotonic solution.

4.4. Materials and methods

4.4.1. 3D-QSAR Studies

The pharmacophore modeling and 3D-QSAR studies were carried out using PHASE version as implemented in the Maestro 11.2.013 modeling package from Schrodinger, installed on a Core i3 1.70 GHz, PC with Windows 7 operating system. A dataset consisting of 58 (hetero)arylethenesulfonyl fluorides as radical scavenging and anti-inflammatory activities were selected for the current study. The chemical structures and IC_{50} values for the complete set of compounds are listed in Table 1. Ligands structures were sketched using the 2D structure draw application and imported on Maestro workspace for energy minimization using the OPLS 2005 force field with the LigPrep module. Conformers for each optimized structure were generated using ConfGen be applying the OPLS-2005 force field method, and the lowest energy conformer was selected for further study.

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Appendix A. Supplementary matarial

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