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Synthesis and Characterization of Biphenyl Based Hydrazones of 1, 2, 4-Triazole Derivatives and their Biological Activities

Cherka Deepthi*, Dr. Shobha Rani

Department of Pharmaceutical Chemistry, UCPSC, Sultanpur, JNTUH, Hyderabad, Telangana

ABSTRACT:

Since the beginning of organic chemistry, heterocyclic chemistry has been at the heart of finding drugs that make life better for people. The main aim of the study is to synthesize the characterization, and evaluation of the anti-inflammatory activity of some novel compounds of biphenyl based hydrazones of 1, 2, 4-triazole derivatives. Based on the results provided above, it was determined that two of the eight compounds in this series, 8b and 8c, exhibited stronger anti-inflammatory effects than the gold-standard medicine, Ibuprofen. These two compounds outperformed the other seven compounds with an inhibition of 80.8% at 3 hours and 82.5% at 5 hours, respectively. Compound 8b had a stronger anti-inflammatory impact.

Keywords: Anti-inflammatory, 1, 2, 4-triazole, Hydrazones.

1. INTRODUCTION

Heterocyclic chemistry has been at the forefront of discovering chemicals that improve human lives since the dawn of organic chemistry. As an example, heterocyclic compounds account for about 70% of all medications in use today. Key intermediates in a great deal of biological processes, they are found all throughout nature. In most cases, novel molecules of biological relevance are developed from heterocyclic compounds that have been isolated from natural sources. Also, the majority of heterocyclic medications are made from simple, easily accessible compounds. To that end, it is very important to synthesize and characterize novel molecular entities that include heterocyclic structures. Investigating this line of inquiry in organic chemistry has many advantages. To begin with, it will be useful in explaining the until unknown inherent chemical behavior of tiny molecules. Second, it will be a huge boon to research into novel synthesis techniques. Thirdly, spectral techniques of characterization of a group of compounds would provide standards for the characterization of other molecules with comparable structures. Lastly, lead compounds for further structural fine-tuning may be discovered by biological examination of the produced molecules. Organic molecules that include sulphur or nitrogen atoms are very important due to the special characteristics that these elements provide.

Azole is one of several chemicals in the vast class known as heterocyclic chemistry. Azoles are heterocyclic compounds with five carbon atoms and one nitrogen, sulphur, or oxygen atom, or at least one non-carbon atom. There are heterocyclic rings like this in it.

The wide range of biological activity shown by azoles—main constituents in several drugs—includes antibacterial, anti-inflammatory, analgesic, antimitotic, anticonvulsive, diuretic, and countless more applications.[2-8]. In the fight against skin disorders and AIDS's secondary symptoms, they are crucial. Plant protection and industrial applications are two other areas where they find usage (leather, wool, fibres). A thorough guidebook detailing their uses and applications is already available, thanks to the field's quick growth.

2. MATERIALS ANS METHODS

Experimental

Present Work

Among the many biological actions recognized for the 1,2,4-triazole derivatives and their mannich bases are antibacterial, anti-inflammatory, analgesic, and countless other applications [9–15]. The need to find new structural leads for less toxic and more effective anti-inflammatory and antibacterial treatments is growing in response to the rising prevalence of drug resistance in these classes of medicines. To create novel chemical entities with promising activity against a wide range of microorganisms, scientists have synthesised several 1,2,4-triazole-based antibacterial drugs.

In addition, several NSAIDs, or nonsteroidal anti-inflammatory medicines, have been created to reduce inflammation. While nonsteroidal anti-inflammatory drugs (NSAIDs) might alleviate inflammation, many of these drugs come with unwanted side effects, such as stomach ulcers [16], kidney

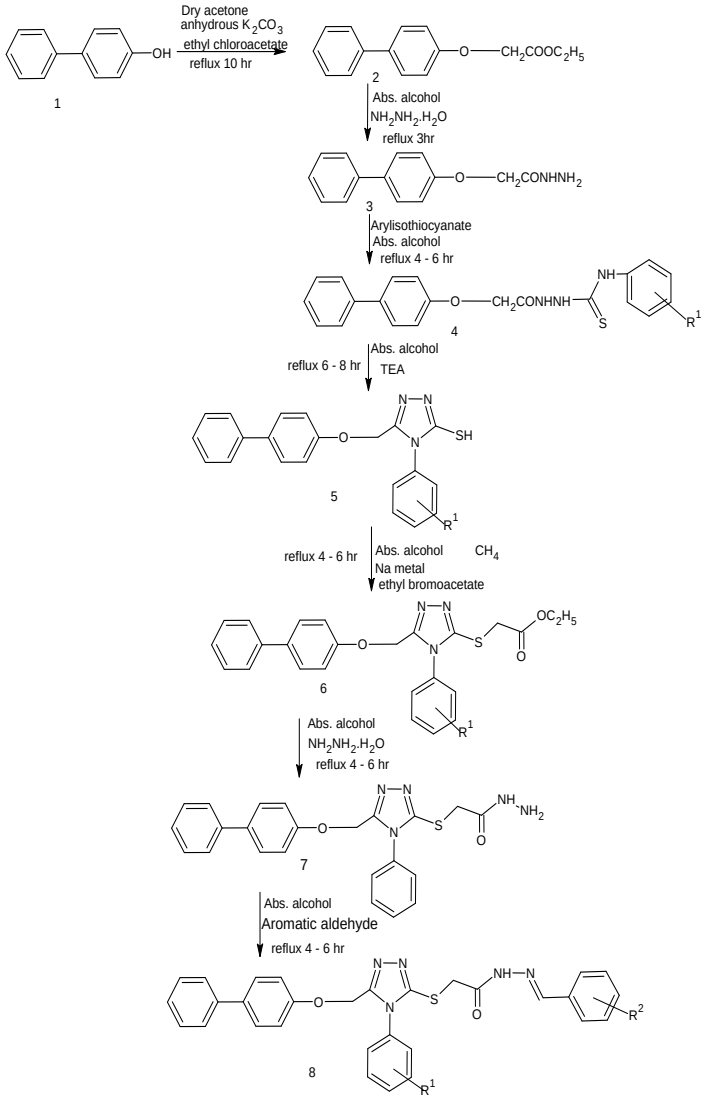
damage [17], and even hepatotoxicity [18]. Many 1,2,4-triazole compounds have been the focus of intense research and development efforts in recent decades [19–21]. Many references in the literature point to nonsteroidal anti-inflammatory drugs (NSAIDs) containing triazole moieties. Among them, 1,2,4-triazole 3-thiol derivatives have garnered a lot of attention and research as of late [22–26].

When an aromatic or heteroaromatic aryl nucleus is substituted into biphenyl derivatives, the majority of nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit superior anti-inflammatory efficacy. Inhibiting the 14 kDa human platelet phospholipase A2 (HP-PLA2) has led several biaryl acid derivatives to be considered as possible anti-inflammatory drugs [27]. Ulceration may be caused by some biphenylic substances that have free carboxyl groups [28-29].

Due to the anti-inflammatory and antimicrobial properties of quinoline, biaryl, and 1,2,4-triazole moieties, we thought it would be interesting to create tiny molecular ligands with a high affinity by conjugating these bioactive pharmacophores. The next four parts will discuss the conjugates' biological activity and how they were synthesised.

Chemistry

Products of commercial origin were used for all compounds (reagent grade). The results are raw, unprocessed melting points obtained with a VEEGO-VMP-DS melting point instrument. A Bruker DPX 400 and 300 1H NMR equipment were used to record the data in CDCl3/DMSO-d6, with TMS serving as the internal standard. The coupling constants (J) and 1H NMR chemical shifts (δ) are listed in ppm and Hz, respectively. Using a Jeol JMS-D 300 apparatus with a JMS 2000 data system and operating at 70 Ev and Maldi-MS (AB-4800), mass spectra were collected. In m/z format, mass spectrometry (MS) results are presented. In order to do the elemental analysis, the Elementar Vario EL III was used. Reported elemental analysis data is in the conventional format of %.



General methods of preparation

Ethyl 2-(biphenyl-4-yloxy) acetate (2) was prepared by reacting p-hydroxybiphenyl (1) with ethylchloroacetate in anhydrous acetone with potassium carbonate. 2-(biphenyl-4-yloxy) acetohydrazide (3) was easily obtained by refluxing the resulting compound with hydrazine monohydrate in absolute alcohol. By reacting with several substituted aryl isothiocyanates in 100% alcohol, compound (3) was subsequently transformed into the appropriate

thiosemicarbazide (53-59). Using triethylamine in pure alcohol, the thiosemicarbazides (4) were cyclized into the corresponding substituted 3-mercapto-1,2,4-triazoles (5). To create the desired compounds, 3-mercapto-1,2,4-triazoles are S-alkylated with various alkyl halides and substituted phenacyl bromides (6). Based on their comprehensive spectrum data, all of the synthesised compounds have been thoroughly characterised. This novel series of compounds was then tested for various biological activities.

***General procedure for synthesis of Ethyl-2-bipheny-4-yloxy-acetate* (2)**

It was combined with 50 mL of anhydrous acetone, 10 mmol of p-hydroxybiphenyl, and 10 mmol of ethylchloroacetate, and then 15 g of K2CO3. For twenty hours, the mixture was refluxed. The reaction was filtered while hot, the filtrate was concentrated under reduced pressure, and the crude product, a 75% yield white flakes with a melting point of 40–42 ºC and an Rf value of 0.64 (n-hexane: ethyl acetate; 6:4), was eventually crystallised from methanol under cool conditions.

***General procedure for synthesis of* 2-(4-phenylphenoxy) acetohydrazide (3)**

An ethanolic mixture containing ten millimoles of (2) and ten millimoles of hydrazine monohydrate was refluxed for four to six hours. Once the reaction was complete, the liquid was cooled, filtered, and recrystallized from alcohol to get the white flakes. Rf = 0.23 (n-hexane: ethyl acetate; 4:6), white flakes, 90% yield, melting point 165–167 ºC.***3.1.3.3 General procedure for synthesis of thiosemicarbazides* (4)**

A 1 mmol solution of arylisothiocyanate was added to a 50 ml 100% alcohol solution of hydrazide (3), and the combination was refluxed for four to six hours. The reaction was cooled to room temperature after being monitored by TLC. The resulting white crystals were filtered and crystallised from alcohol to get pure thiosemicarbazide (4).

***General method for synthesis of 5-[(biphenyl-4-yloxy)methyl]4-aryl-3-mercapto- (4H)-1,2,4-triazole* (5)**

The reaction mixture was refluxed for 4-8 hours after adding 1 millilitre of triethyl amine to a 50 millilitre solution of thiosemicarbazide (4) (5 mmol) in absolute alcohol. The pure 3-mercapto-1,2,4-triazoles were obtained by cooling the reaction mixture to room temperature and then concentrating the solution under reduced pressure (25 mL). The resulting precipitate was then washed with cold water, dried, and crystallised in ethanol after the reaction was monitored by TLC.

***General method for synthesis of 1(Aryl)-2-[5-{(biphenyl-4-yloxy)methyl}4-aryl-3- mercapto -(4H)-1,2.4-triazol-3-ylthio)] ethanone/ethane* (6)**

The reaction mixture was refluxed for 1-6 hours after adding sodium metal (0.5 mmole) and various substituted phenacyl bromide (0.5 mmole) to a solution of 3-mercapto-1,2,4-triazole (5, 0.5 mmole) in absolute ethanol (50 ml). Reaction was carried out under reduced pressure (25 ml) after TLC monitoring was complete. The resulting solution was cooled, filtered, washed with water, dried, and recrystallized from dichloromethane (DCM) and methanol to obtain the pure compound (6).

***General procedure for synthesis of hydrazide* (7)**

The hydrazine monohydrate (10 mmol) and compound 6 (10 mmol) ethanolic solution was refluxed for four to five hours. Once the reaction was finished, the liquid was cooled and poured over crushed ice. The resulting precipitate was then filtered, rinsed with cold water, dried, and recrystallized from alcohol.

***General procedure for synthesis of hydrazones of 1,2,4-triazole* (8)**

The reaction mixture was refluxed for four to six hours after adding various aromatic aldehydes in equimolar ratios to a solution of hydrazide 7 (1 mmol) in absolute alcohol (50 mL). A few drops of glacial acetic acid were also added. To obtain pure hydrazone 8, the reaction mixture was cooled to room temperature and concentrated under reduced pressure after being monitored by TLC. The resulting solution was then poured onto crushed ice. After filtering off the precipitate, it was washed with cold water, dried, and crystallized in ethanol.

Biological evaluation

Anti-inflammatory activity

We tested the anti-inflammatory activity [30] of all the newly synthesised compounds against acute paw oedema caused by carrageenan. Rats in the first group received a placebo, another group had a conventional dosage of 10 mg/kg of ibuprofen suspension, and the third group received an equimolar dose of the test compounds' suspension in comparison to the standard treatment. Subcutaneous injections of 0.1 mL of 1% carrageenan in normal saline were administered to the sub-plantar area of the right hind paw of the animals 30 minutes later. At 0, 1, 3, and 5 hours, the plethysmometer was used to measure the paw volume. At the respective time intervals, the oedema amounts in the drug-treated groups were compared to those in the control group. The following equation was used to compute the percent oedema inhibition from the mean effect in the control and treated animals.

The inhibition percentage is equal to one hundred times (1 - Vt/Vc).

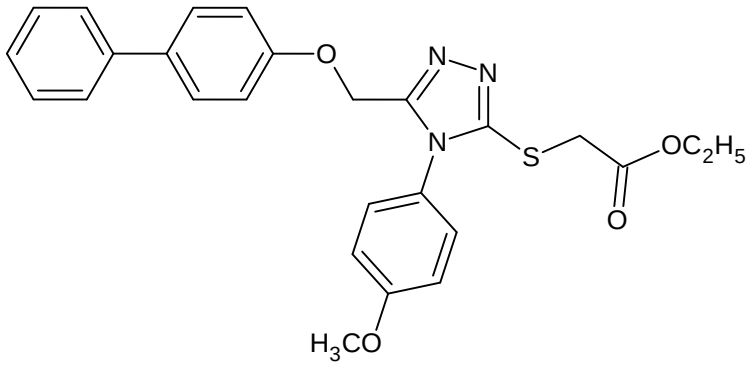
The average rise in the test paw volume, denoted as Vt,

Vc is the average growth in paw volume among the rats in the control group.

RESULT AND DISCUSSION

Physiochemical and spectral analysis

Ethyl2-[5{(4-biphenyloxy)methyl}-4-(4-methoxyphenyl)-4H-1,2,4-triazol-3-ylthio] acetate



Yield: 79%; White Crystals, **m.p.** 139-141 ºC; **Rf** = 0.57 (CHCl3: MeOH; 9:1).

IR (KBr) cm^{-1}: 3062, 2989, 1673, 1611, 1241, 1093.

^{1}H NMR (300 MHz, CDCl$_3$) : δ 1.26 (t, *J* = 7.2 Hz, 3H, CH_2-**CH_3**), 3.85 (s, 3H, O-CH_3), 4.08 (s, 2H, S-CH_2), 4.20 (q, *J* = 7.2 Hz, 2H, O-CH_2), 5.09 (s, 2H, O-CH_2), 6.95-7.01 (m, 4H), 7.26-7.31 (m, 3H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.50-7.53 (m, 4H, Ar-H).

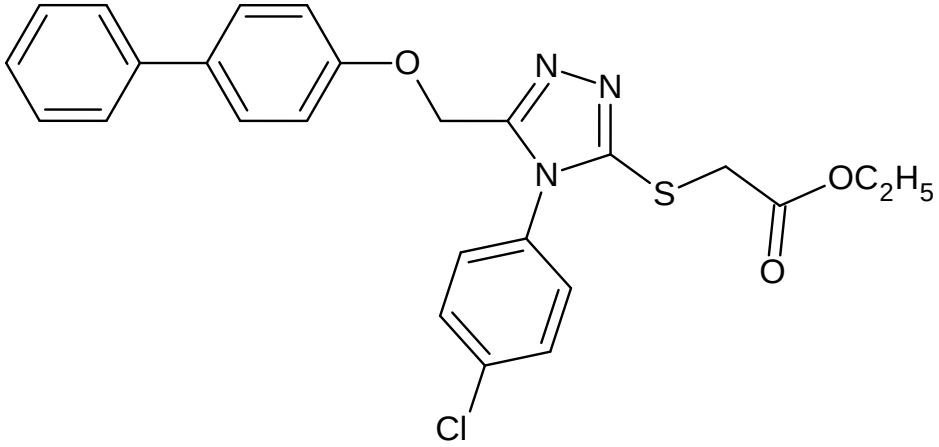
Maldi-MS (*m/z*): 475 (M+), 476 (M^++1)

Elemental Analysis: Calculated for molecular formula $C_{26}H_{25}N_5O_4S$:

Calculated: C, 65.67; H, 5.30; N, 8.84

Found: C, 65.57; H, 5.29; N 8.83%

Ethyl-2-[5{(4-biphenyloxy)methyl}-4-(4-chlorophenyl)-4H-1,2,4-triazol-3- ylthio]acetate



Yield: 73%; White Crystals, **m.p.** 129-131ºC; **Rf** = 0.56 (CHCl3: MeOH; 9:1).

IR (KBr) cm^{-1}: 3058, 3025, 1675, 1603, 1241, 1107.

1H NMR (300 MHz, CDCl$_3$): δ 1.26 (t, *J* = 7.2 Hz, 3H, CH_2-CH_3), 4.09 (s, 2H, S-CH_2), 4.20 (q, *J* = 7.2 Hz, 2H), 5.09 (s, 2H, OCH_2), 6.94 (d, *J* = 8.7 Hz, 2H), 7.25-7.43 (m, 5H), 7.46-7.52 (m, 6H, Ar-H).

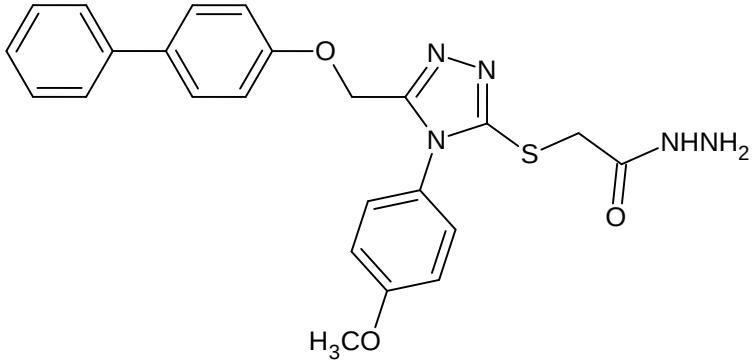
Maldi-MS (*m/z*): 480 (M+), 482 (M^++2)

Elemental Analysis: Calculated for molecular formula $C_{26}H_{25}N_5O_4S$:

Calculated: C, 65.67; H, 5.30; N, 8.84

Found: C, 65.57; H, 5.29; N 8.83%

2-[5{(4-biphenyloxy)methyl}-4-(4-methoxyphenyl)-4H-1,2,4-triazol-3-ylthio] acetohydrazide



Yield:80%; White Crystals, **m.p.** 143-145 ºC; **Rf** = 0.53 ($CHCl_3$: MeOH; 8:2).

IR (KBr) cm^{-1}: 3503, 1683, 1603, 1507.

^{1}H NMR (300 MHz, CDCl3) : δ 1.62 (brs, 2H, -NH2), 3.85 (s, 3H, O-CH3), 4.08 (s, 2H, S-CH2), 5.07 (s, 2H, O-CH2), 6.95-7.01 (m, 4H), 7.25-7.32 (m, 3H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.46-7.52 (m, 4H, Ar-H), 8.91 (s, 1H, NH).

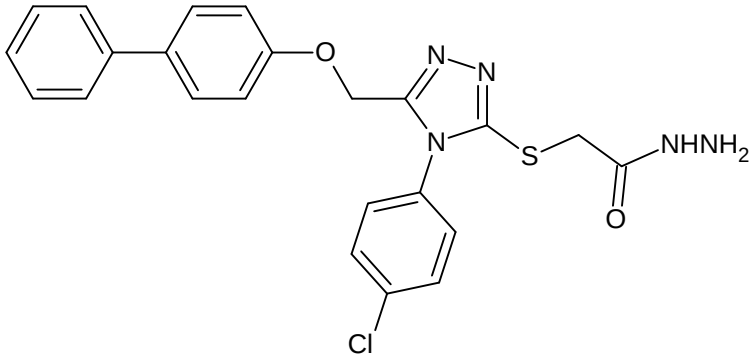
Maldi-MS (*m/z*) : 461 (M+), 462 (M^++1)

Elemental Analysis: Calculated for molecular formula $C_{24}H_{23}N_5O_3S$

Calculated: C, 62.46; H, 5.02; N, 15.17

Found: C 62.39; H 5.01; N 15.15%

2-[5{(4-biphenyloxy)methyl}-4-(4-methoxyphenyl)-4H-1,2,4-triazol-3-ylthio] acetohydrazide



Yield: 89%; White crystals, **m.p.** 138-140 ºC; **Rf** = 0.54 (CHCl3: MeOH; 9:1).

IR (KBr) cm^{-1}: 3246, 3058, 2690, 1668, 1241, 1107.

^{1}H NMR (300 MHz, CDCl3) : δ 2.95 (brs, 2H, NH-**NH2**), 3.94 (s, 2H,S-CH_2), 5.11 (s, 2H, O-CH_2), 6.96 (d, *J* = 8.4 Hz, 2H), 7.30-7.32 (m, 3H), 7.43 (t, *J* = 7.8 Hz, 2H),7.49- 7.54 (m, 6H, Ar-H), 8.14 (s, 1H, N-H).

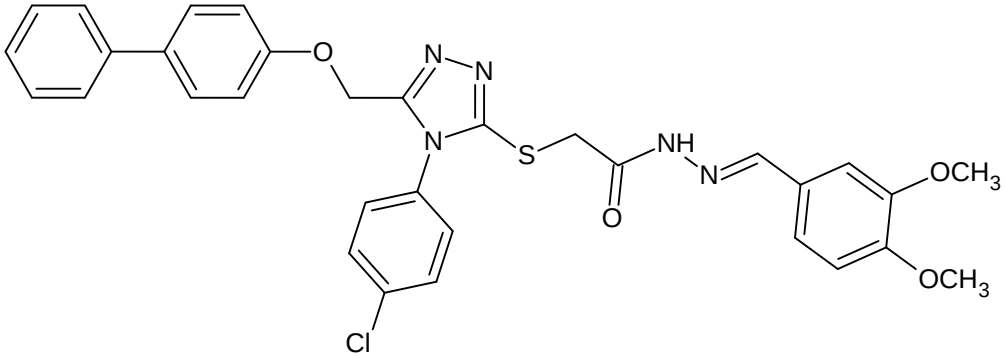
Maldi-MS (*m/z*): 465 (M+), 467 (M^++2)

Elemental Analysis: Calculated for molecular formula $C_{23}H_{20}ClN_5O_2S$

Calculated: C, 59.29; H, 4.33; N, 15.03

Found: C 59.21; H 4.31; N 15.05%.

N'-(3,4-dimethoxybenzylidene)-2-[5-{(4-phenylphenoxy)methyl}-4-(4-chlorophenyl) -4H-1,2,4-triazol-3-ylthio]acetohydrazide



Yield: 68%; White crystals; **m.p.**183-185 ºC; **Rf** = 0.46 (CHCl3: MeOH; 9:1).

IR (KBr) cm^{-1}: 3216, 3054, 2936, 1684, 1603, 1515, 1492, 1377, 1268, 1134, 1093, 1024, 835, 764, 699.

^{1}H NMR (300 MHz, CDCl3) : δ 3.91-3.99 (m, 6H, 2 O-CH3), 4.15 (s, 2H, SCH2), 5.14 (s, 2H, O-CH2), 6.82-7.30 (m, 6H), 7.33-7.62 (m, 11H), 8.13 (s, 1H, N-H).

^{13}C NMR (100 MHz, CDCl3) : δ 34.17, 55.91, 59.89, 108.46, 110.47, 115.05, 123.01, 126.46, 127.02, 128.28,128.36, 128.48, 130.10, 130.39, 135.28, 137.04, 140.29, 145.59, 149.14, 151.92, 152.23, 152.72, 154.16, 156.86, 164.51, 169.01.

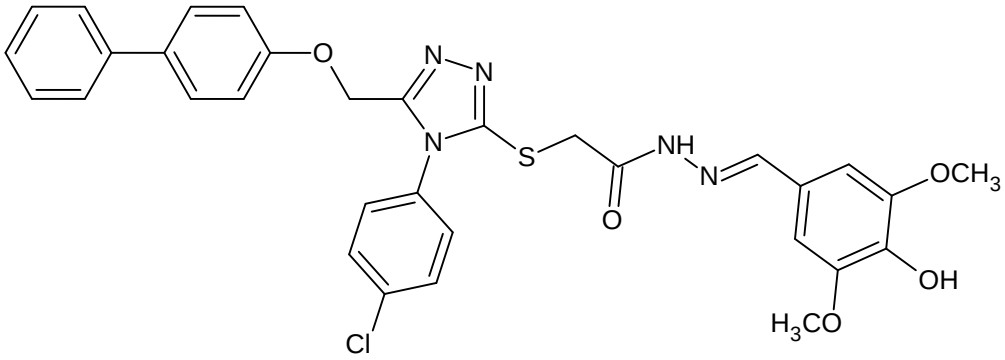
Maldi-MS (*m/z*): 614 (M+), 616 (M^{+}+1).

Elemental Analysis: Calculated for molecular formula $C_{32}H_{28}ClN_5O_4S$.

Calculated: C, 62.58; H, 4.60; N, 11.40

Found: C 62.56; H 4.61; N, 11.38%.

N'-(3,5-di-methoxy-4-hydroxybenzylidene)-2-[5-{(4-phenylphenoxy)methyl}-4-(4- chlorophenyl)-4H-1,2,4-triazol-3-ylthio]acetohydrazide



Yield: 63%; White crystals; **m.p.**191-193 ºC; **Rf** = 0.41 (*n*-hexane : ethyl acetate; 4:6).

IR (KBr) cm^{-1} : 3180, 3054, 2932, 1662, 1592, 1519, 1494, 1378, 1129, 1005, 836, 760.

^{1}H NMR (300 MHz, CDCl3) : δ 3.89-3.84 (s, O-CH_3, 6H), 3.90 (s, 2H, S-CH_2), 5.09 (s, 2H, O CH_2), 6.89 (s, 1H), 7.03- 6.95 (m, 5H), 7.31-7.27 (m, 4H), 7.40 (t, *J* =

7.2 Hz, 2H), 7.51-7.48 (m, 4H), 8.07 (s, 1H, NH), 11.51 (s, 1H, OH).

^{13}C NMR (75 MHz, CDCl3) : δ 38.56, 55.71, 59.15, 114.44, 124.10, 125.93, 126.20, 127.43, 127.78, 127.90, 128.09, 129.29, 129.45, 134.25, 135.51, 139.65, 144.77, 147.21, 152.29, 156.23, 163.09, 167.90.

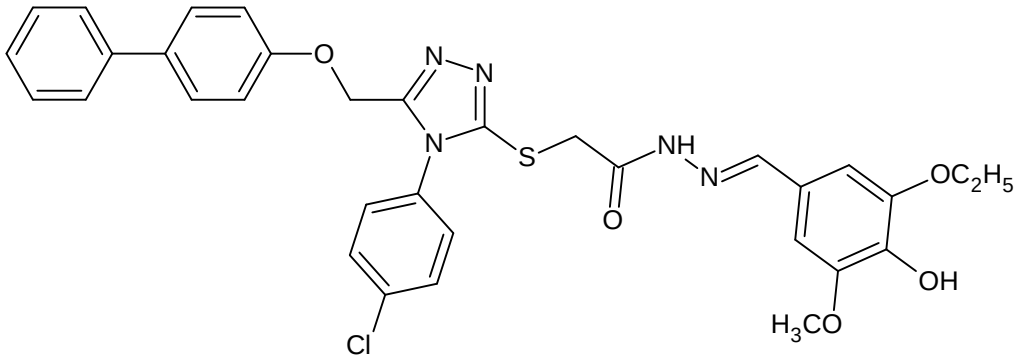
Maldi-MS (*m/z*) : 630 (M+), 632 (M^{+}+2)

Elemental Analysis: Calculated for molecular formula $C_{32}H_{28}ClN_5O_5S$.

Calculated: C, 61.00; H, 4.48; N, 11.11

Found: C 61.04; H 4.47; N 11.12%.

N'-(3-ethoxy,4-hydroxybenzylidene)-2-[5-{(4-phenylphenoxy)methyl}-4-(4- chlorophenyl)- 4H-1,2,4-triazol-3-ylthio]acetohydrazide



Yield: 69%; White crystals; **m.p.**175-177 ºC; **Rf** = 0.54 (CHC_{l3}: MeOH; 9:1).

IR (KBr) cm-1 : 3204, 3066, 1678, 1603, 1492, 1378, 1276, 1089, 834, 764.

^{1}H NMR (300 MHz, CDCl3) : δ 1.31 (t, *J* = 6.9 Hz, 3H,-CH3), 3.93 (q, *J* = 6.8 Hz, 2H, O-CH2), 4.05 (s, 2H, S-CH2), 5.14 (s, 2H, O-CH2), 6.80-6.88 (m, 4H), 6.94 (d, *J* = 7.8

Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 2H), 7.31-7.43 (m, 10H), 8.00 (s, 1H, N-H), 11.37 (s, 1H, OH).

^{13}C NMR (100 MHz, CDCl3) : δ 14.61, 35.33, 59.67, 64.26, 114.91, 121.60, 125.55, 126.36, 126.66, 127.86, 128.29, 128.38, 128.55, 129.73, 129.85, 131.07, 134.38, 135.83, 139.97, 144.99, 146.83, 146.92, 148.84, 149.21, 151.47, 152.53, 156.64, 156.70, 163.51, 168.00.

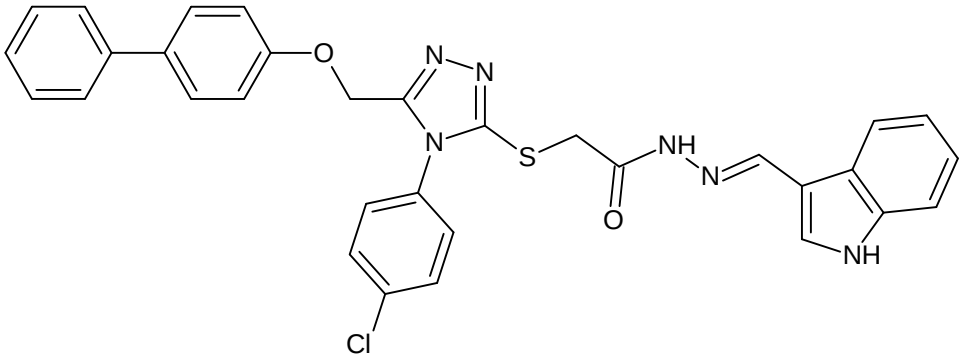
Maldi-MS (*m/z*) : 614 (M+), 615 (M^{+}+1).

Elemental Analysis: Calculated for molecular formula $C_{32}H_{28}ClN_5O_4S$.

Calculated: C, 62.58; H, 4.60; N, 11.40

Found: C 62.59; H 4.61; N 11.41%

(E)-N'-(1H-indol-3-yl)methylene-2-[5-{(4-phenylphenoxy)methyl}-4-(4- chlorophenyl)-4H-1,2,4-triazol-3-ylthio]acetohydrazide



Yield: 69%; light yellow flakes, **m.p.** 177-179 ºC; **Rf** = 0.38 ($CHCl_3$: MeOH; 9:1).

IR (KBr) cm^{-1}: 3474, 1671, 1613, 1248, 1092.

^{1}H NMR (300 MHz, CDCl3) : δ 4.54 (s, 2H, S-CH2), 4.98 (s, 2H, O-CH2), 6.82 (d, *J* = 6 Hz, 2H), 7.20-7.05 (m, 3H), 7.40-7.29 (m, 14H), 8.00 (s, 1H, N-H), 9.88 (1H, s, OH).

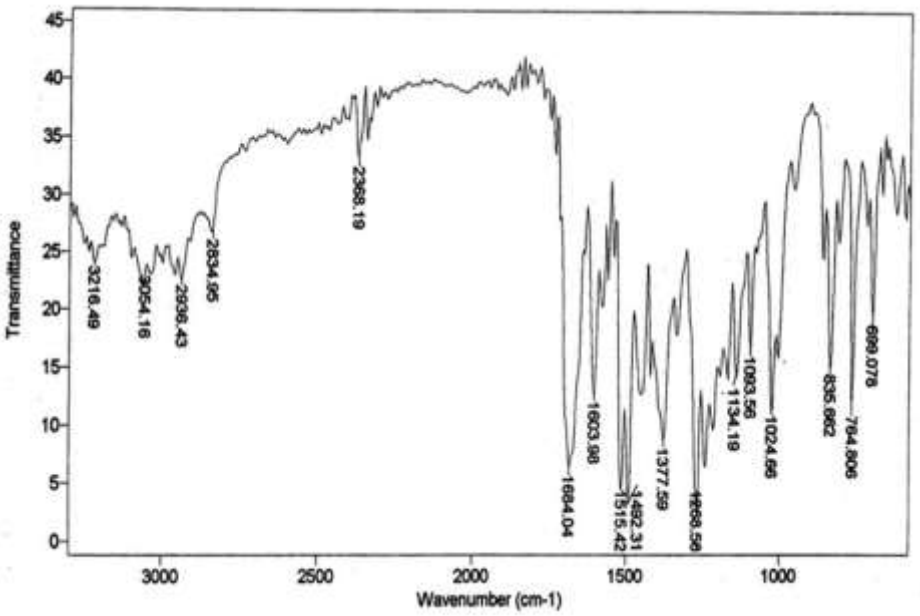
^{13}C NMR (100 MHz, CDCl3) : δ 35.30, 59.90, 111.28, 111.93, 115.28, 120.61, 121.59, 122.67, 124.03, 126.26, 126.86, 127.75, 128.85, 129.08, 129.83, 130.66, 131.61, 133.57, 134.83, 137.11, 139.61, 141.45, 144.38, 151.65, 151.98, 156.91, 162.26,167.38.

Maldi-MS (*m/z*): 593 (M+), 595 (M^{+}+2).

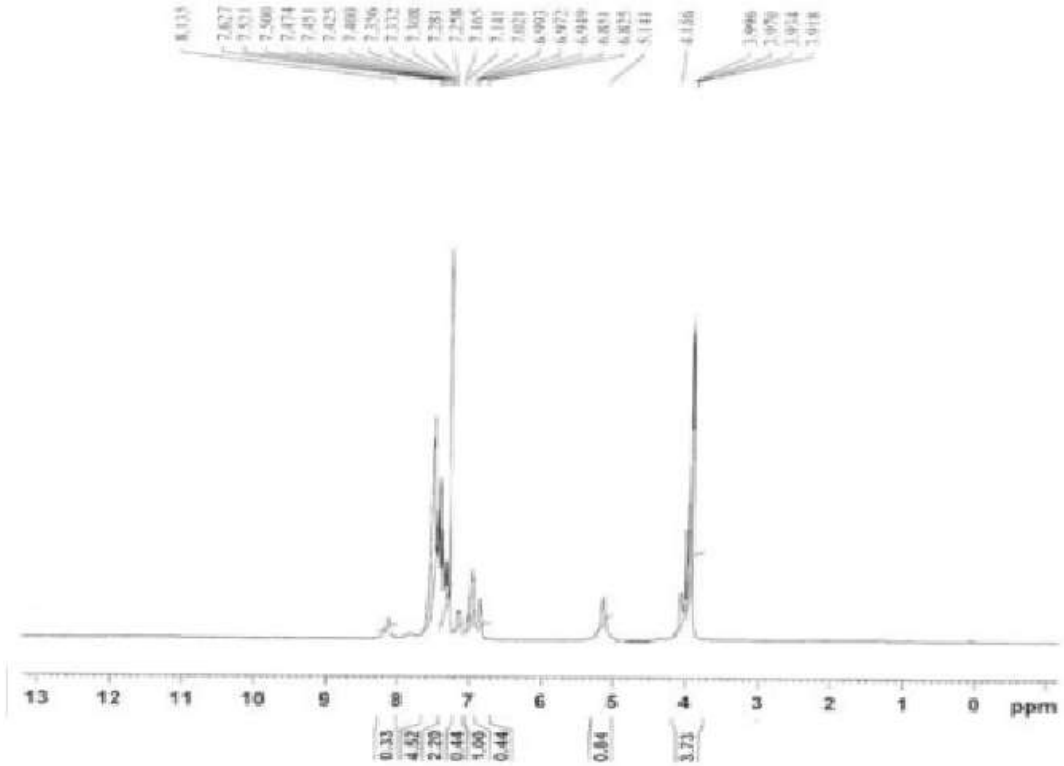
Elemental Analysis: Calculated for molecular formula $C_{32}H_{25}ClN_6O_2S$.

Calculated: C, 64.80; H, 4.25; N, 14.17

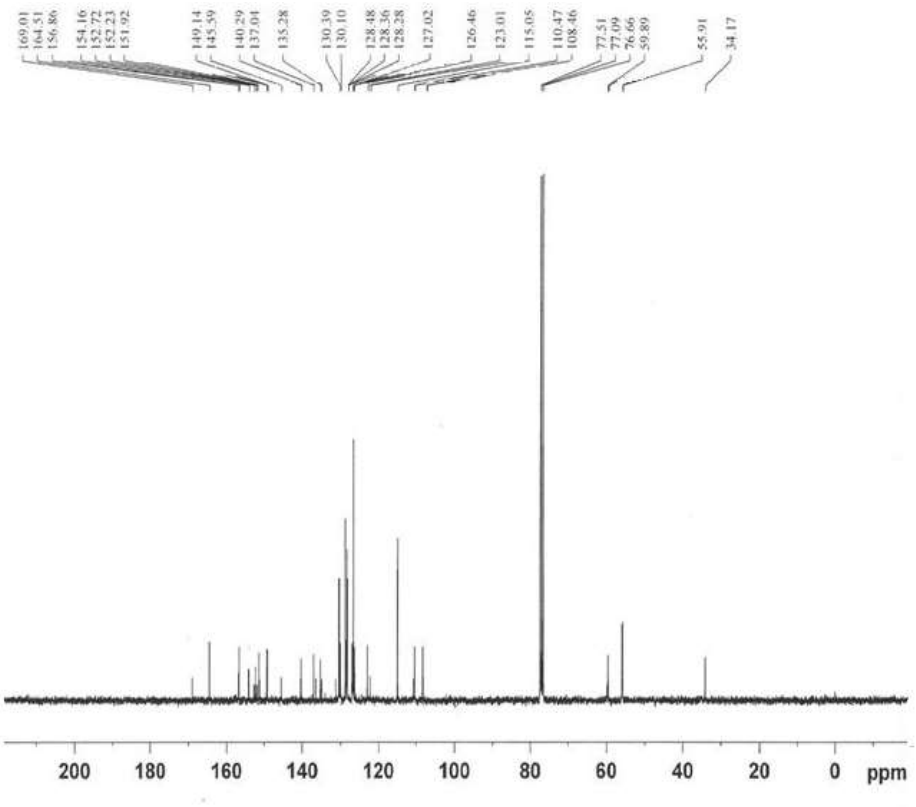
Found: C 64.83; H 4.26; N 14.19%.



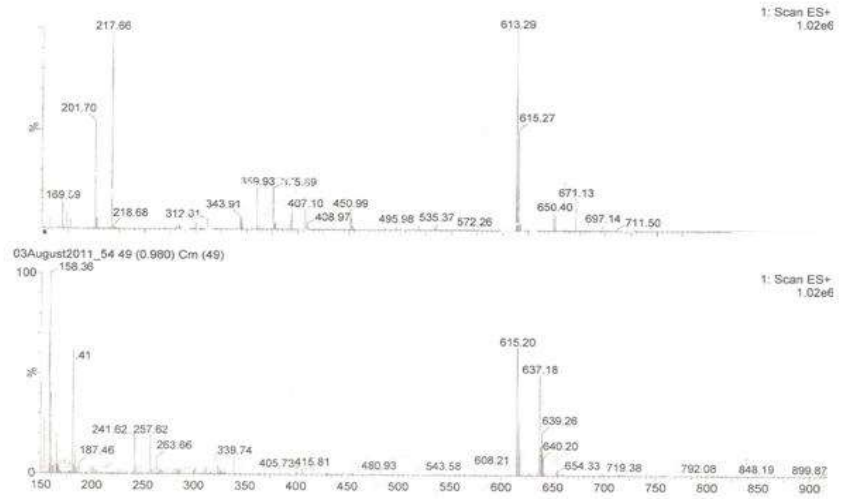
IR spectrum of compound **8b**



1H NMR spectrum of compound **8b**



13C NMR spectrum of compound **8b**



Mass spectrum of compound **8b**

Biological activity

4.2.1. Anti-inflammatory activity

Table 4.1 Anti-inflammatory activity of biphenyl based hydrazones of 1,2,4-triazole derivatives

Compounds	**Change in paw oedema volume (mL) After drug treatment**		**Anti-inflammatory activity % Inhibition**	
	3h	5h	3h	5h
Control	0.624±0.046	0.571±0.030	-----	-----
Ibuprofen	0.12±0.032***	0.10±0.010***	80.8	82.5
6a	0.34±0.021*	0.30±0.031*	45.6	47.5
6b	0.40±0.044ns	0.45±0.022ns	35.9	42.49
7a	0.48±0.022ns	0.45±0.022ns	23.1	21.2
7b	0.40±0.039ns	0.43±0.042ns	35.9	24.7
8a	0.35±0.022*	0.41±0.030ns	44	28.2
8b	0.10±0.036***	0.10±0.025***	**84**	**83**
8c	0.33±0.033**	0.18±0.030***	**47.2**	**68.5**
8d	0.35±0.042*	0.25±0.021**	44	56.3

Data analyzed by one way ANOVA followed by Dunnett's ´t´ test (n=6), *p<0.05, **p<0.01 & ***P<0.001 significantly different from standard; ns, not significant

Albino Wistar rats (150-200 g) were used to test the anti-inflammatory effectiveness of all the synthesised compounds against carrageenan-induced paw edoema. The findings on the anti-inflammatory activity are summarised in figure 4.1 and table 4.1. In terms of paw oedema at 3 and 5 hours, respectively, two of the compounds (8b and 8c) were shown to be considerably active (84, 83% inhibition) compared to the standard medication Ibuprofen (80.8 and 82.5%), whereas compound 8d exhibited modest activity. For this study, we used a rat model of carrageenan-induced paw edoema and analysed the data using a one-way ANOVA followed by Dunnett's test.

5. Conclusion

The data shown above led to the conclusion that among the eight compounds in this series, two 8b and 8c had superior anti-inflammatory action compared to the gold standard medication Ibuprofen (80.8 and 82.5 % inhibition at 3 and 5 hours, respectively) compared to the other seven compounds. A more robust anti-inflammatory effect was seen in compound 8b.

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