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Design, synthesis and pharmacological assay of novel azo derivatives of dihydropyrimidinones

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Abstract: The present work deals with the synthesis of some novel azo derivatives of dihydropyrimidinones. The structures of newly synthesized compounds were established on the basis of their FTIR, 1H NMR, Mass spectrometry and elemental analysis data results. The synthesized agents were assessed for their in vivo anti-inflammatory activity on the Wistar albino rats. The compounds were also screened for their anthelmintic activity on Indian earthworms and anti-bacterial activity against some Gram-positive and Gram-negative strains of bacteria. This pharmacological activity appraisal unveils that among all the compounds screened, compounds 4b, 4c and 4g were found to have potential anti-inflammatory activity. Furthermore, compounds 4b and 4c exhibited appreciable anthelmintic properties while compounds 4b and 4d showed leading anti-bacterial activity against the selected pathogenic strains of bacteria.

Subjects: Drug Design & Development; Microbiology; Pharmaceutical Medicine

Keywords: azo derivatives; anti-inflammatory; anthelmintic; anti-bacterial

1. Introduction

Azo derivatives are a class of chemical compounds that are continuously receiving attention in scientific research (Kirkan & Gup, 2008; Seferoğlu, 2009). The azo derivatives in the present century display remarkable applications in each and every stratum. Most of the azo compounds whatsoever have been used as dyes. Perhaps there would be a very few applications other than use of the dyes.
Constant research done during the twentieth century and thereafter have resulted in every imaginable form of colour of dye. Modern dyes serve more than just as being pretty. They have become indispensable tools for a variety of industries. From acting as colorants for plastics, textile dyeing industries and the highly sophisticated biotechnology industry, dyes are touching our life everywhere (Chakraborty, Saha, & Dutta, 2010). Nowadays, various synthetic azo compounds are manufactured to meet the requirements of each type of industry. They are widely used in different fields (Gong, Gao, Wang, Zhao, & Freeman, 2002; Hinks, Freeman, Nakpathom, & Sokolowska, 2000; Wojciechowski & Gumulak, 2003; Wojciechowski, Wyrębak, & Gumulak, 2003) such as medicines (Pielesz, Baranowska, Rybak, & Włochowicz, 2002; Rudyk et al., 2003; Wainwright, 2008), cosmetics, paints (Ahmed, Hay, Bushell, Wardell, & Cavalli, 2008), automobile industry and in analytical chemistry (Mittal, Kurup, & Mittal, 2007).

However, an unavoidable fact that still wanders in the minds of researchers is that the textile materials undergo biological degradation and it appears that about 40% of the damage is due to the effect of micro-organisms. The bacterial action results in the reduced mechanical strength of a material, colour change, stains and stale odour. Therefore, it becomes essential to manufacture newer azo compounds that would combat this problem and would extend the service life of these materials and avoid damage caused as such by the biological degradation. Earlier literature shows that the incorporation of an azo linkage in a heterocyclic compound has resulted into enhanced anti-bacterial properties of the compound as a whole (Khedr, Gaber, & Abd El-Zaher, 2011; Nikhil, Pratik, & Manoj, 2011; Swati, Karnawat, Sharma, & Verma, 2011). Moreover, apart from acting as good colouring and anti-bacterial agents, these synthetic azo compounds are now an important ingredient in many of the medical tests. Many of the tests that are carried out on patients use a dye to get accurate results. Dyes occupy an integral part of microbiology (Wainwright, 2001). These are used to make the micro-organisms distinctly visible and differentiate them. Also, the azo compounds find biological applications in medicine as anti-tumor (Farghaly & Abdallah, 2008), anti-diabetic (Garg & Prakash, 1972), antiseptic (Browning, Cohen, Ellingworth, & Gulbransen, 1926), anti-inflammatory compounds, as hypnotic drugs for the nervous system (Seferoğlu & Ertan, 2008) and many such useful chemotherapeutic properties (Bae, Freeman, & El-Shafei, 2003; Thakor, Patel, Patel, & Patel, 2007; Swati et al., 2011). Some of the azo dye compounds are known to act in a site specific manner for drug delivery in the colon to combat diseases such as colitis and irritable bowel syndrome (Mooter, Maris, Samyn, Augustijns, & Kinget, 1997). Thus, to develop new pharmacologically active azo compounds with enhanced biological properties, remains need of the hour. Herein, an effort has been made to synthesize such azo compounds with pharmacological potential.

2. Materials and method

2.1. Materials

All common reagents and solvents were used as obtained from commercial supplies without further purifications. Melting points of the synthesized compounds were taken by one end open capillary tubes melting point apparatus and are uncorrected. Infra Red (IR) spectra were recorded on Shimadzu FTIR 8400S spectrophotometer (KBr) and NMR spectra were recorded on Bruker-Avance (400 MHz) spectrophotometer using DMSO-d$_6$ solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on Waters Micromass Q-ToF Micro Mass Spectrometer. Elemental analysis (C, H and N) for the synthesized compounds was obtained using EU Elemental Analyzer. Thin layer chromatography (TLC) was performed using Silica gel G obtained from Merck and the spots were visualized under and iodine vapours. Developing solvents used were petroleum ether (60–80°C) and ethyl acetate (7:3).

2.2. Method (Scheme 1)

2.2.1. Procedure for the synthesis of ethyl 4-((4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate (1)

The desired compound was synthesized using the reported method (Oliver Kappe, 1997).
2.2.2. Procedure for the synthesis of 4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carbohydrazide (2)
The above dihydropyrimidinone (1) (0.01 mol) was dissolved in absolute ethanol (10 ml) and to this hydrazone hydrate (0.01 mol) was added. The reaction mixture was refluxed for around 6–7 h. The completion of reaction was monitored by TLC. After completion, the reaction mixture was allowed to stand overnight and the resulting solid obtained was filtered, dried and crystallized from ethanol.

2.2.3. Synthesis of azo derivatives of dihydropyrimidinones 4(a–g)
The azo derivatives were synthesized according to the method as described under. It follows a two-step synthetic protocol.
Step I: Diazotization

A mixture of carbohydrazide (2) (0.016 mol) and concentrated hydrochloric acid was stirred until a clear solution was obtained. This solution was cooled to 0–5°C and a solution of sodium nitrite in 10-ml water was then added dropwise, maintaining the temperature below 5°C. The resulting mixture was stirred for an additional 30 min in an ice bath and was then buffered (pH 5.0) with solid sodium acetate trihydrate.

Step II: Coupling

Corresponding aromatic hydroxyl compound (0.016 mol) was dissolved in 8 ml 10% sodium hydroxide, and cooled to 0–5°C in an ice bath. This solution was then gradually added to the cooled diazonium salt solution and the resulting mixture was stirred at 0–5°C for 1 h. The resulting crude precipitate was filtered, washed several times with cold water and recrystallized from hot chloroform to yield azo compound 4(a–g).

The melting points and corresponding percentage yields of compounds 4(a–g) is shown in Table 1.

The spectral data of the corresponding compounds are as follows:

Analysis of \( N'(1\text{-hydroxynaphthalen-4-ylimino})-4\text{-}(4\text{-}(dimethylamino)phenyl)-1,2,3,4\text{-tetrahydro-6-methyl-2-oxopyrimidine-5-carbohydrazide (4a)}

IR (KBr, cm\(^{-1}\)): 1461 (N=N), 1681 (C=O), 2977 (C–H), 3061 (Ar C–H), 3316 (N–H). \( ^1\)H NMR (\( \delta \) ppm): 2.47 (s, 3H, CH\(_3\)), 3.11 (s, 3H, CH\(_3\)), 5.35 (d, \( J = 7.5 \), 1H, CH), 6.52 (s, 1H, NH), 6.27–8.19 (m, 10H, Ar–H). MS: \( m/z \) 444. Anal. Calcd (C\(_{24}\)H\(_{24}\)N\(_6\)O\(_3\)): 64.85; H, 5.44; N, 18.91. Found: 64.80; H, 5.41; N, 18.89.

Table 1. Corresponding melting points and percentage yields of the synthesized compounds 4(a–g)

| Compounds | Molecular formula | Melting point (°C) | Yield (%) |
|-----------|-------------------|--------------------|-----------|
| 4a        | C\(_{24}\)H\(_{24}\)N\(_6\)O\(_3\) | 152–154            | 74        |
| 4b        | C\(_{24}\)H\(_{24}\)N\(_6\)O\(_3\) | 158–160            | 75        |
| 4c        | C\(_{24}\)H\(_{24}\)N\(_6\)O\(_3\) | 154–157            | 80        |
| 4d        | C\(_{24}\)H\(_{24}\)N\(_6\)O\(_3\) | 147–150            | 71        |
| 4e        | C\(_{24}\)H\(_{24}\)N\(_6\)O\(_3\) | 155–159            | 76        |
| 4f        | C\(_{24}\)H\(_{24}\)N\(_6\)O\(_3\) | 149–152            | 73        |
| 4g        | C\(_{24}\)H\(_{24}\)N\(_6\)O\(_3\) | 161–163            | 72        |

Analysis of \( N'(2\text{-hydroxynaphthalen-1-ylimino})-4\text{-}(4\text{-}(dimethylamino)phenyl)-1,2,3,4\text{-tetrahydro-6-methyl-2-oxopyrimidine-5-carbohydrazide (4b)}

IR (KBr, cm\(^{-1}\)): 1447 (N=N), 1656 (C=O), 2981 (C–H), 3093 (Ar C–H), 3188 (N–H). \( ^1\)H NMR (\( \delta \) ppm): 2.32 (s, 3H, CH\(_3\)), 3.19 (s, 3H, CH\(_3\)), 5.27 (d, \( J = 7.3 \), 1H, CH), 6.71 (s, 1H, NH), 7.14–8.61 (m, 10H, Ar–H). MS: \( m/z \) 444. Anal. Calcd (C\(_{24}\)H\(_{24}\)N\(_6\)O\(_3\)): C, 64.85; H, 5.44; N, 18.91. Found: C, 64.82; H, 5.42; N, 18.92.

Analysis of \( N'(5\text{-hydroxy-2-oxo}-2\text{H-chromen-8-ylimino})-4\text{-}(4\text{-}(dimethylamino)phenyl)-1,2,3,4\text{-tetrahydro-6-methyl-2-oxopyrimidine-5-carbohydrazide (4c)}

IR (KBr, cm\(^{-1}\)): 1438 (N=N), 1633 (C=O), 2989 (C–H), 3058 (Ar C–H), 3293 (N–H). \( ^1\)H NMR (\( \delta \) ppm): 2.25 (s, 3H, CH\(_3\)), 3.22 (s, 3H, CH\(_3\)), 5.28 (d, \( J = 7.4 \), 1H, CH), 6.59 (s, 1H, NH), 6.12–7.29 (m, 8H, Ar–H). MS: \( m/z \) 462. Anal. Calcd (C\(_{24}\)H\(_{24}\)N\(_6\)O\(_3\)): C, 59.73; H, 4.79; N, 18.17. Found: C, 59.74; H, 4.74; N, 18.15.

Analysis of \( N'(7\text{-hydroxy-2-oxo}-2\text{H-chromen-8-ylimino})-4\text{-}(4\text{-}(dimethylamino)phenyl)-1,2,3,4\text{-tetrahydro-6-methyl-2-oxopyrimidine-5-carbohydrazide (4d)}

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IR (KBr, cm⁻¹): 1452 (N=N), 1667 (C=O), 2964 (C–H), 3109 (Ar C–H), 3428 (N–H). ¹H NMR (δ ppm): 2.39 (s, 3H, CH₃), 3.16 (s, 3H, CH₃), 5.44 (d, J = 7.4, 1H, CH), 6.63 (s, 1H, NH), 6.10–7.30 (m, 8H, Ar–H). MS: m/z 462. Anal. Calcd (C₂₃H₂₂N₆O₅): C, 59.73; H, 4.79; N, 18.17. Found: C, 59.70; H, 4.76; N, 18.14.

Analysis of N′-(3-formyl-4-hydroxyphenylimino)-4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carbohydrazide (4e)

IR (KBr, cm⁻¹): 1443 (N=N), 1674 (C=O), 2936 (C–H), 3084 (Ar C–H), 3277 (N–H). ¹H NMR (δ ppm): 2.20 (s, 3H, CH₃), 2.94 (s, 3H, CH₃), 5.61 (d, J = 7.2, 1H, CH), 6.66 (s, 1H, NH), 6.27–8.19 (m, 7H, Ar–H). MS: m/z 422. Anal. Calcd (C₂₁H₂₂N₆O₄): C, 59.71; H, 5.25; N, 19.89. Found: C, 59.70; H, 5.21; N, 19.86.

Analysis of N′-(8-hydroxyquinolin-5-ylimino)-4-(4-(dimethylamino)phenyl)-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carbohydrazide (4f)

IR (KBr, cm⁻¹): 1436 (N=N), 1651 (C=O), 2956 (C–H), 3067 (Ar C–H), 3106 (N–H). ¹H NMR (δ ppm): 2.27 (s, 3H, CH₃), 3.24 (s, 3H, CH₃), 5.11 (d, J = 7.5, 1H, CH), 6.57 (s, 1H, NH), 6.82–7.98 (m, 9H, Ar–H). MS: m/z 445. Anal. Calcd (C₂₃H₂₃N₇O₃): C, 62.01; H, 5.20; N, 22.01. Found: 62.04; H, 5.17; N, 21.98.

3. Pharmacological investigation

3.1. Anti-inflammatory activity

The in vivo anti-inflammatory activity appraisal was done by the carrageenan-induced hind paw edema method (Winter, Risley, & Nuss, 1962). The experimental protocol for anti-inflammatory activity was approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India (SPCP/2013/595–2). Wistar albino rats were divided into nine groups of five animals each. Group I, which served as the control, was given only 0.5% w/v carboxymethyl cellulose (CMC); whereas traditional NSAID Diclofenac (10 mg/kg), used as standard reference drug and the synthesized test compounds (30 mg/kg) were administered orally to the rats of Group II (standard) and the other groups, respectively. After 1 h, all the rats were injected with 0.1 ml of 1% carrageenan solution (freshly prepared in normal saline) in the subplantar aponeurosis of left hind paw to induce inflammation and the volume of injected paw

Table 2. Anti-inflammatory activity of compounds 4(a–g)

| Compounds       | Paw volume (ml) ± SEM | Inhibition (%) |
|-----------------|-----------------------|---------------|
| Control         | 0.55 ± 0.009          |               |
| Diclofenac      | 0.54 ± 0.011          | 86.32         |
| 4a              | 0.64 ± 0.013          | 30.77         |
| 4b              | 0.67 ± 0.009          | 53.85         |
| 4c              | 0.69 ± 0.007          | 47.00         |
| 4d              | 0.70 ± 0.012          | 39.31         |
| 4e              | 0.63 ± 0.006          | 31.62         |
| 4f              | 0.65 ± 0.009          | 48.71         |
| 4g              | 0.61 ± 0.006          |               |

Note: Data were given in mean ± SEM and analyzed by ANOVA followed by Dunnett’s multiple comparison test (n = 6). *p < 0.05 compared to standard drug.
was measured using plethysmometer immediately (at 0 h). The paw volume was again measured at an interval of 1 h up to 3 h (Table 2). The average paw volume in a group of treated rats was compared with control group and the percentage inhibition of edema was calculated by using the formula:

\[
\text{Percent inhibition} = \left(1 - \frac{V_t}{V_c}\right) \times 100
\]

where \(V_t\) is the mean paw volume of the test and drug treated rats and \(V_c\) is the mean paw volume of the control.

The results obtained are expressed as mean ± SEM (standard error of mean) of five rats. Statistical differences of control and test groups were carried out using the Analysis of Variance (ANOVA) followed by Dunnett’s test. The difference in results was considered significant when \(p < 0.05\).

### 3.2. Anthelmintic activity

The in vitro anthelmintic activity was carried out on adult Indian earthworms, *Pheretima postuma*. The worms were collected from local moist place and prior assay; the worms were washed with normal saline so as to remove all faecal matter. They were divided into nine groups of five worms each. Distilled water was used as control while Piperazine citrate (10 mg/ml) was used as reference standard for this study (Gbolaide & Adeyemi, 2008; Lal, Chandra, Raviprakash, & Sabir, 1976; Mali & Wadekar, 2008; Mali, Mahajan, & Patil, 2005). Three different concentrations of 5, 10 and 15 mg/ml for the compounds and standard drug solution were freshly prepared and poured into Petri dishes. Worms were then introduced into the Petri dishes and observations were made for the time taken for paralysis and death of worms. Paralysis was said to occur when the worms do not revive even in normal saline. Death was confirmed when the worms showed zero movement when shaken vigorously or when dipped in warm water (50°C) followed with fading away of their body colour. The results obtained are expressed as mean ± SEM (standard error of mean). Statistical differences were carried out using the ANOVA and was considered significant when \(p < 0.05\).

Observations obtained are represented in Table 3.

### 3.3. Anti-bacterial activity

The in vitro anti-bacterial activity of the newly synthesized compounds 4(a–g) was estimated by the well-diffusion method using Hi-Media agar medium against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumonia*, *Proteus vulgaris* and *Pseudomonas aeruginosa* strains of bacteria. In the method herein, the Petri plates of agar medium were prepared by pouring melted agar inoculated with above-mentioned strains of bacteria. Wells were scooped out of the agar medium contained

![](image)

Table 3. Anthelmintic activity of compounds 4(a–g)

| Compounds | 5 mg/ml | 10 mg/ml | 15 mg/ml |
|-----------|---------|----------|----------|
|           | Time taken for paralysis (min) | Time taken for death (min) | Time taken for paralysis (min) | Time taken for death (min) | Time taken for paralysis (min) | Time taken for death (min) |
| Control   | -       | -        | -        | -        | -        | -        |
| Piperazine citrate | -       | -        | 21 ± 0.9 | 59 ± 0.2 | -        | -        |
| 4a        | 65 ± 0.6 | 89 ± 0.7 | 60 ± 0.5 | 76 ± 0.5 | 42 ± 0.2 | 63 ± 0.7 |
| 4b        | 62 ± 0.7 | 86 ± 0.8 | 59 ± 1.0 | 81 ± 0.8* | 48 ± 0.5* | 59 ± 0.4 |
| 4c        | 61 ± 0.5* | 84 ± 0.9 | 59 ± 0.6 | 78 ± 0.7 | 45 ± 0.1 | 58 ± 0.8 |
| 4d        | 73 ± 0.9 | 96 ± 0.6 | 69 ± 0.4 | 92 ± 0.7 | 51 ± 0.7* | 62 ± 0.6 |
| 4e        | 72 ± 1.2 | 95 ± 0.2* | 67 ± 0.3 | 89 ± 0.3 | 52 ± 0.3 | 64 ± 0.4 |
| 4f        | 66 ± 0.8 | 81 ± 0.5 | 61 ± 0.7* | 83 ± 0.6 | 43 ± 0.4 | 60 ± 0.5 |
| 4g        | 71 ± 0.3 | 90 ± 0.9 | 65 ± 0.9 | 81 ± 0.4 | 47 ± 0.5 | 61 ± 0.3* |

Note: Results were given in mean ± SEM and analyzed by ANOVA.

*\(p < 0.05\) compared to standard drug.
in these Petri plates. Each test compound (1 mg) was dissolved in ethanol (1 ml, 1,000 μg/ml), which was used as sample solution. Sample size for all the compounds was fixed at 0.1 ml. The test compound solution (0.1 ml) was added in the wells and the Petri plates were subsequently incubated at 37°C for 24 h. Ampicillin and Streptomycin were used as reference drugs and ethanol as the negative control. The zones of inhibition thus produced by each compound were measured and compared with the control and the consequent results are depicted in Table 4.

4. Results and discussion

4.1. Chemistry

Successful syntheses of azo derivatives of dihydropyrimidinones have been carried out as per the reaction formulated in Scheme 1 and the products were obtained in good yield. Formation of target compounds was confirmed by recording their IR, 1H NMR, mass spectral data and the elemental analyses. IR spectra of the compounds show absorption band within 1,461–1,436 cm⁻¹ due to the characteristic N=N group. The NMR data of all compounds exhibit a multiplet in the region of 6.10–8.21 ppm due to the presence of aromatic protons. Sharp singlet within 2.17–2.47 ppm range is a characteristic of the methyl protons of the 4-(dimethylamino)benzaldehyde. The other signals and peaks of the IR and 1H NMR are in complete agreement with the assigned structures. The mass spectra of the compounds displayed a molecular ion peak at appropriate m/z values, which corresponded well with the respective molecular formula. Satisfactory analytical results were obtained for the elemental analysis of the synthesized compounds.

4.2. Pharmacological investigation

The anti-inflammatory activity of all the synthesized compounds 4(a–g) was calculated using the carrageenan-induced hind paw edema method. The compounds were tested at an effective dose level of 30 mg/kg. Observed results reveal that, all the synthesized compounds shielded the rats from carrageenan-induced inflammation and compounds show significant anti-inflammatory activity against control at the said concentration after 3 h. The compounds exhibited anti-inflammatory activity ranging from 30.77 to 53.85% (Table 2), whereas standard drug Diclofenac showed 86.32% inhibition after 3 h. Compounds 4b, 4c and 4g were found to be potent anti-inflammatory agents with an appreciable percent inhibition of 53.85, 47.00 and 48.71%, respectively, while 4d and 4f were found to be moderately active agents with corresponding percent inhibition of 39.31 and 44.44%.

The synthesized compounds were also tested for their in vitro anthelmintic activity and the anthelmintic study was carried out on the adult Indian earthworm, Pheretima posthuma. Compounds were tested at three different concentrations 5, 10 and 15 mg/ml for which acceptable activity was obtained. Piperazine citrate was used as standard reference drug. It was observed that, at higher
dose level, the compounds gave comparatively enhanced activity. Compounds 4b and 4c were found to produce eventual death of the worms in lesser time and were said to be good anthelmintic agents, where as 4f and 4g were found to be moderate anthelmintic agents.

Moreover, the compounds were screened for their in vitro anti-bacterial activity against S. aureus, B. subtilis, E. coli, K. pneumonia, P. vulgaris and P. aeruginosa strains of bacteria using the well-diffusion method. Compounds 4b and 4d were found to be highly active against all the tested strains of bacteria showing the broadest spectrum of anti-bacterial activity while 4e and 4f were found to be moderately active against the selected pathogens when compared to reference drug Ampicillin and Streptomycin at a dose of 1,000 μg/ml.

Thus, the observed results of the in vivo and in vitro assay infer that the synthesized azo compounds possess appreciable anti-inflammatory, anthelmintic and anti-bacterial properties.

5. Conclusion
To conclude, a successful synthesis of a series of novel azo derivatives of dihydropyrimidinones was achieved in good yield. The pharmacological activity evaluation reveals the synthesized compounds as good bioactive moieties. Compounds 4b, 4c and 4g gave good anti-inflammatory activity with reference to standard drug Diclofenac while compounds 4b and 4c exhibited appreciable anthelmintic property at concentrations of 5, 10 and 15 mg/ml when compared to the standard reference drug Piperazine citrate. The in vitro anti-bacterial assay performed conclude the compounds 4b and 4d as active anti-bacterial agents with reference to standard drug Ampicillin and Streptomycin at a dose of 1,000 μg/ml, and thus these synthesized azo compounds can be used as dyes with pharmacological properties in various sectors.

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