Pak. j. sci. ind. res. Ser. A: phys. sci. 2017 **60**(3) 122-127

Schiff Bases Derived from 1-Aminoanthraquinone: A New Class of Analgesic Compounds

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(received June 2, 2017; revised June 20, 2017; accepted June 21, 2017)

Abstract. A series of Schiff bases **1-17** were synthesised by way of a facile condensation between 1-aminoanthraquinone with a variety of carbonyl compounds in the presence of a catalytic amount of dodecatungstosilicic acid/P_2O_5 under solvent free conditions at room temperature. These were charachterised by ^{1}H- and ^{13}C-NMR, LCMS, FTIR and elemental analyses. All the compounds were screened for their analgesic activity using hot plate thermal stimuli method at dose of 10 and 30 mg/kg. Diclofenac sodium was used as a reference drug. All the compounds at dose of 10 and 30 mg/kg body weight showed the significant ($p<0.05$) increase in latency time as compared to control (normal saline). Compound **5** showed excellent activity after 120 min of drug administration (10 mg/kg) of body weight. Compound **10** was found to be potent (10.48±1.19s, 11.27±1.2s and 10.24±1.9s) at dose of 30 mg/kg at 30, 60 and 120 min, respectively when compared to the standard drug. Compound **6** (10.13±0.4s) was also found to be an excellent analgesic compound at a dose of 30 mg/kg at 120 min. However, the studies on analgesic activity revealed that some of the target compounds may be strong candidates as an analgesic drug.

Keywords: schiff bases, 1-aminoanthraquinone, analgesic compound

Introduction

Pain is a typical sensory experience that may be described as the unpleasant awareness of a noxious stimulus or bodily harm. It is initiated by stimulation of nociceptors in the peripheral or central nervous system, or by damage to or malfunction of the peripheral or CNS. The term analgesic means a drug that selectively relieves pain by acting in the CNS or peripheral pain mechanism without significantly altering consciousness (Bennett and Villa, 2000). Non-steroidal anti-inflammatory drugs (NSAIDs) are common medication for the treatment of pain, inflammation and fever. However, the significant side effects have been shown with a long term usage of NSAIDs including serious gastrointestinal lesion, kidney injury and cardiovascular risk. During the last century many analgesics drugs have been reported to possess undesirable side effects and hence, injurious to human health. This necessitated the need to look for new effective and safe analgesic drugs. Moreover, the Schiff bases constituted of heterocycles have attracted attention due to their broad spectrum biological activities including antibacterial (Faizul *et al*., 2007; More *et al*., 2001; El-Masry *et al*., 2000; Baseer *et al*., 2000; Pandeya *et al*., 1999), antifungal (Singh and Dash, 1998), antitumor (Hodnett and Dunn, 1970), anticancer (Desai *et al*., 2001), herbicidal (Samadhiya and Halve, 2001), antiproliferative (Nawrocka *et al*., 2006), anti-convulsant (Verma *et al*., 2004; Kaplan and Rizon, 1980), antioxidant (Fareed *et al*., 2013a; 2013b; Rada and Leto, 2008; Almasirad *et al*., 2006), anti-malarial (Tsafack *et al*., 1996; Clarke and Eaton, 1990) and analgesic drugs.

In view of the wide applications of Schiff bases in the drug design, a facile one pot synthesis (Fareed *et al*., 2013c) of Schiff bases **1-17** has been in the present study reported. Direct condensation of 1-aminoanthraquinone with a variety of carbonyl compounds was done in the presence of catalytic amount of dodecatungstosilicic acid/P_2O_5 (scheme 1). All the synthesized compounds were subjected to pharmacological screening and showed varying degrees of analgesic activity. However, the studies on analgesic activity revealed that some of the target compounds may be strong candidates as an analgesic drug.

Materials and Methods

Apparatus. The melting points were recorded in glass capillary using Gallenkamp MF-370 melting point

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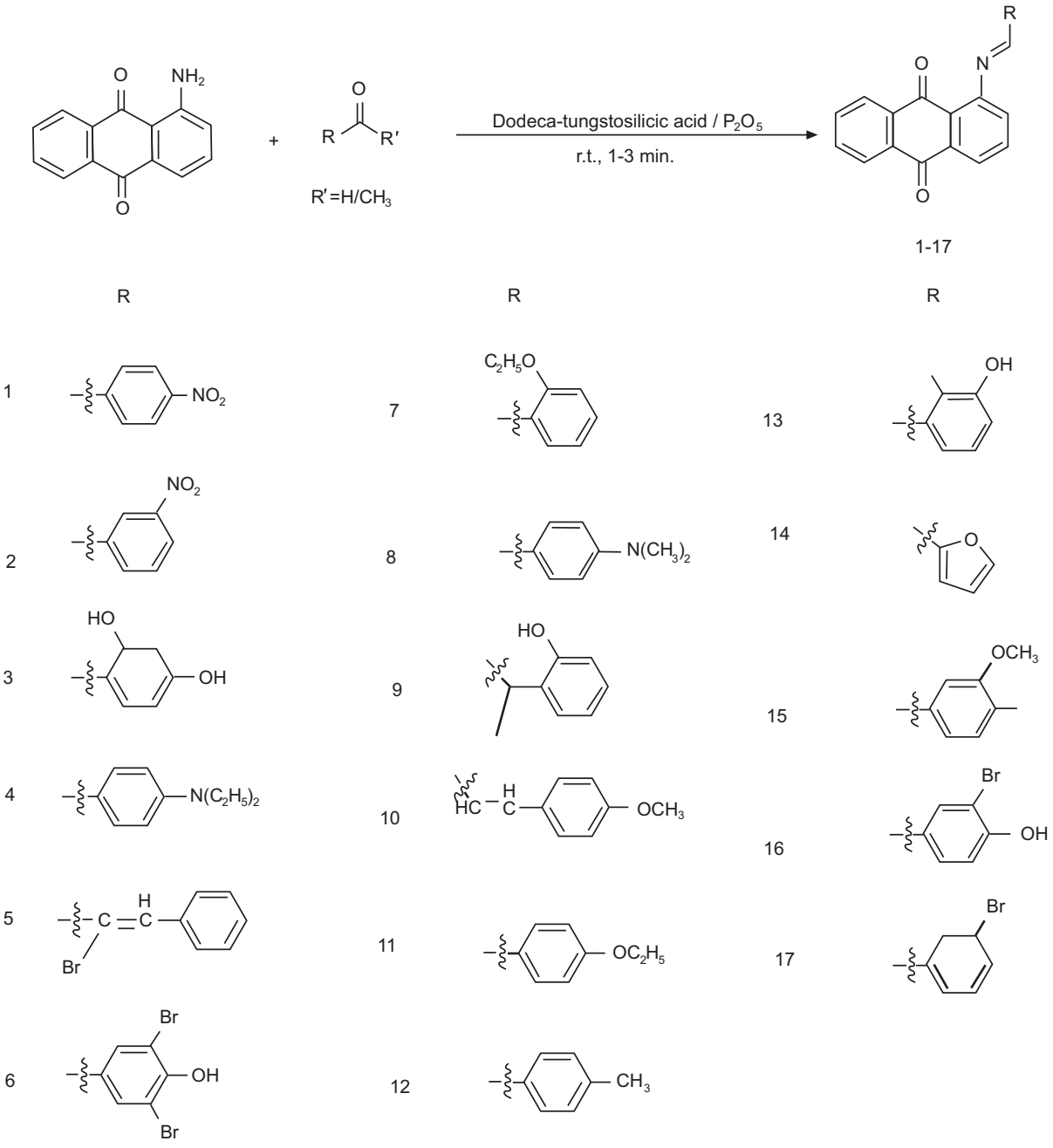
apparatus and are uncorrected. ^{1}H-NMR (300MHz) and ^{13}C-NMR (75MHz) spectra were recorded on Bruker AV-300 NMR Spectrometer in DMSO-d_6 with trimethyl silane (TMS) as an internal standard. IR spectra were recorded on Nicolet Avatar 300 DTGS. Mass spectra were recorded on a Finnigan LCQ Advantage Max. Elemental analyses were performed on a Carlo Erba Strumentazion-Mod-1106 instrument. The purity of compounds was determined by using thin layer chromatography (TLC) on pre-coated silica gel glass plates (Kieselgel 60, 254, E. Merck, Germany), visualized under UV at 254 and 365 nm or in iodine vapours.

General method for the synthesis of Schiff bases 1-17. A mixture of 1-aminoanthraquinone (1 mmol), carbonyl compounds (1 mmol) and $H_{84}O_{40}SiW_{12}/P_2O_5$ (0.2 g, 1mol% of 1-aminoanthraquinone/P_2O_5) as a



Scheme 1. Structures of synthesized Schiff bases **1-17**.

catalyst were ground under solvent free conditions at room temperature for 1-3 min (scheme 1). Crushed ice was added to afford precipitates of the Schiff bases. In order to remove catalyst, the product was washed several times with ice cooled water. The solid products were obtained in excellent yield (Fareed *et al*., 2013d).

Analgesic activity. ***Animals.*** Wistar rats weighing between 100-170 g were used for the analgesic studies. The animals were of either sex and maintained under 22 ± 1 °C with a controlled dark and light cycle (12 h: 12 h), with food and water *ad libitum*. All the experimental animals and protocol had been made according to the guidelines and approval from local ethical committee as per agreement with the Declaration of Helsinki.

***Analgesic testing*.** In the present study analgesia was assessed by thermal nociception through the hot/cold plate device (model no: 35100, UGO Basile, Italy). This apparatus was switched on to heat the surface of the hot plate to a constant temperature of 55 ± 0.5 °C. The rat of each group was dropped on the hot plate (20 cm diameter), which was surrounded by a clear acrylic protective casing (25 cm height with an open top) so as to obtain its response to electrical heat induced pain stimulus. Rats were divided into 14 groups each comprising of six animals. The sample was given orally with the help of feeding canula in a dose of 10 and 30 mg/kg body weight. The experimental animals received diclofenac sodium (50 mg/kg) as standard drug and 0.9% saline as control. The initial readings were taken immediately before administration of test drugs followed by intervals of 30, 60, 120 and 180 min, respectively. The rat paw withdrawal latency, reflected by hind paw licking, flicking, or jumping, was recorded as reaction time (in sec) (Lanthers *et al*., 1992).

Percent analgesic score was calculated as,

$$PAS = T_b\text{-}T_a/T_b \times 100$$

where:

T_b = reaction time before drug administration
T_a = reaction time after drug administration

Statistical analysis. The data are expressed as mean values ± SEM. The time of latency in the hot plate test and significant differences were obtained by using oneway analysis of variance (ANOVA) and Turkey's as posthoc test, with $p<0.05$ and $p<0.01$ as statistically significant. Statistical tests were carried out using SPSS version 20.0 statistical software.

Results and Discussion

Chemistry. The targeted compounds **1-17** were synthesised according to the previously reported methodology as described in the experimental, and subsequently characterised by LCMS, ^{1}H- and ^{13}C-NMR, IR, and CHN analyses. Their ^{1}H-NMR spectra showed the signal of proton of the azomethine moiety (–N=CH-Ar) in the range of 7.4-8.9 ppm, while the aromatic protons appeared as a multiplet in the range of 6.74-7.90 ppm. In IR spectra the stretching of N=C appeared in the region of 1511-1545 cm^{-1}.

Analgesic activity. In the evaluation of analgesic efficacy of compounds the most common protocol is hot plate method. All the synthesised Schiff bases were tested at doses of 10 and 30 mg/kg body weight and showed significant ($p<0.05$) increase in latency time as compared to the control. A maximum effect was established at 180 min after drug administration. Diclofenac sodium was used as a standard drug and normal saline as control. The results of analgesic activity are presented in Tables 1-2, respectively.

The compound **6** bearing 3,5-dibromo-4-hydroxyphenyl and compound **12** *p*-methyl phenyl substituents showed potent activity (9.30±1.56s and 9.26±1.18s), respectively after 30 min of 10 mg/kg of drug administration compared to the standard drug. Activity of compound **6** and 3,5-dibromo-4-hydroxyphenyl substituent sustained at a level of 9.86 ± 0.6s after 60 min. Compound **5** containing α-bromocinnamyl group showed excellent activity after 120 min of drug administration (10 mg/kg). Compound **15** containing 3-methoxy-4-hydroxyphenyl group also showed significant activity (7.2±0.46s) after 180 min of 10 mg/kg. Rest of the compounds showed moderate analgesic activity at 10 mg/kg of dose administration in comparison to diclofenac sodium as shown in Table 1. Compounds **1** having *p*-nitro phenyl substituent and compound **9** bearing 2-hydroxyacetophenyl group showed significant activity at a dose of 30 mg/kg after 30 min (9.7±1.22s and 9.11±0.67s), respectively. Compound **8** also showed good analgesic activity after 60 and 120 min of dose administration of 30 mg/kg. Compound **10** containing *p*-methoxycinnamyl group was found to be potent (10.48 ± 1.19s, 11.27 ± 1.2s and 10.24 ± 1.9s) at a dose of 30 mg/kg at time intervals of 30, 60 and 120 min, respectively. Compounds **1** and **5** showed significant activity after 120 min (9.17±1.3s and 9.73±1.6s), respectively. Compound **6** (10.13±0.4) was also found to be an excellent analgesic compound

Table 1. Analgesic activity by hot plate method at dose of 10 mg/kg

Compounds	Reaction time in sec ± SEM*				
	0 min	30 min	60 min	120 min	180 min
Control (normal saline)	7.13±0.18	6.23±0.55	5.76±0.2	4.83±0.2	4.69±0.2
Diclofenac sodium (50 mg/kg)	7.49±0.32	10.81±0.15	11.3±0.2	11.93±0.2	11±0.1
1	5.54±0.27	5.83±0.46	5.86±0.52	6.24±0.56	5.69±0.36
2	5.67±0.5	6.79±0.58	6.44±0.31	6.77±0.7	6.1±0.25
3	5.91±1.14	6.16±1.27	6.4±1.4	6.03±1.1	6.53±1.2
4	5.54±0.3	6.55±0.29	6.81±0.4	5.89±0.58	5.46±0.8
5	7±0.68	7.4±0.2	8.73±0.9	10.13±1.7**	8.93±1.88**
6	7.97±0.9	9.30±1.56*	9.86±0.6*	8.67±1.28*	9.57±0.99**
7	5.11±0.04	6.27±0.17	7.48±0.98	7.53±0.7	6.03±0.68
8	5.29±0.35	6.08±0.77	7.83±2.6	7.17±0.27	6.61±0.2
9	7.77±1.4	8.06±1.27	7.84±0.9	7.58±0.5	8.97±1.27**
10	7.47±0.18	8.94±1.9**	8.76±2.5	8.36±2.9*	6.65±1.8
11	5.45±1.2	4.91±0.7	5.03±0.6	5.47±0.59	6.06±0.9
12	8.16±1.1	9.26±1.18**	8.22±0.8	6.34±0.4	6.33±0.5
13	3.9±0.5	4.2±0.5	4.8±0.5	6.3±0.8	6.4±1.1
14	4.06±0.2	4.6±0.2	5.4±0.08	6.2±0.1	6.5±0.38
15	4.73±0.4	5.1±0.6	6.0±0.6	6.6±0.7	7.2±0.46*
16	3.9±0.6	4.3±0.58	4.1±0.2	5.2±0.5	7.1±0.5
17	3.7±0.4	3.8±0.57	4.3±0.4	5.1±1.6	6.9±1.6

All values are mean ± SEM, $n = 6$; *SEM = standard error of mean; One way analysis of variance (ANOVA) followed by Tukey's as post-hoc test whereas $p<0.05$ was considered significant. $p<0.01$ was considered to be more significant; *$p<0.05$; **$p<0.01$ as compared with control group.

Table 2. Analgesic activities by hot plate method at dose of 30 mg/kg

Compounds	Reaction time in sec ± SEM*				
	0 min	30 min	60 min	120 min	180 min
Control	7.13±0.18	6.23±0.55	5.76±0.2	4.83±0.2	4.69±0.2
Diclofenac sodium (50 mg/kg)	7.49±0.32	10.81±0.15	11.3±0.2	11.93±0.2	11± 0.1
1	6.89±0.44	9.7±1.22**	7.9±0.5	9.17±1.3**	8.63±1.4*
2	4.71±0.41	5.15±0.19	7.21±1.2	7.63±0.6	4.92±0.9
3	6.40±1.37	7.04±1.03	6.85±1.6	7.51±2.5	5.54±1.8
4	5.36±1.03	5.07±0.4	6.65±0.7	5.74±0.4	5.22±1.3
5	6.56±0.45	6.96±0.4	7.09±0.5	9.73±1.6**	9.1±1.8**
6	6.97±0.14	8.4±0.817*	8.5±0.7	10.13±0.4**	8.8±1.6*
7	5.83±0.32	7.6±1.12	8.33±1.4	8.06±0.7*	8.03±1*
8	5.33±0.33	6.98±0.46	9.8±1.6**	8.52±0.2*	7.27±0.2
9	7.47±1.21	9.11±0.67**	8.94±0.3*	7.83±0.6	7.7±0.7
10	7.47±0.18	10.48±1.19**	11.27±1.2**	10.24±1.9**	7.03±0.5
11	5.42±0.94	6.16±0.68	6.09±0.4	5.46±0.6	5.83±0.7
12	7.97±1.10	7.88±0.65	8.02±0.7	7.86±0.8	7.56±0.6
13	3.9±0.5	4.1±0.5	4.6±0.5	4.8±0.49	5.2±0.5
14	4.06±0.26	4.4±0.3	4.9±0.2	5.3±0.2	4.6±0.38
15	4.7±0.48	5±0.5	5.4±0.48	5.8±0.48	6.1±0.4*
16	3.9±0.6	4.2±0.6	5.1±0.9	5.6±0.9	5.9±0.9
17	3.7±0.4	4.2±0.36	4.5±0.39	5.1±0.39	5.6±0.37

All values are Mean ± SEM; $n = 6$, *SEM = standard error of mean; One way analysis of variance (ANOVA) followed by Tukey's as post-hoc test whereas $p<0.05$ was considered significant; $p<0.01$ was considered to be more significant; *$p<0.05$; **$p<0.01$ as compared with control group.

at a dose of 30 mg/kg at 120 min. Compound **15** also showed significant activity (6.1±0.4s) after 180 min of 30 mg/kg dose. Rest of the compounds showed moderate to weak analgesic activity at 30 mg/kg of dose administration in comparison to diclofenac sodium as shown in Table 2. The SAR study suggests that the analgesic activity enhance with electron donating substituents and extension in conjugation at phenyl group. In this study all the compounds did not reveal any undesirable side effects or behavioral changes. No mortality was observed in a period of about 30 days.

Conclusion

Compounds **5**, **6**, **10** and **12** exhibit very significant analgesic activity at a dose of 10 mg/kg. Compounds **9** and **10** showed potent activity at a dose of 30 mg/kg. In view of the results described here, Schiff bases derived from 1-amino-anthraquinone may leads to a good source of analgesic drug.

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