Synthesis and Antimicrobial Activity of New Synthesized Paracetamol Derivatives and Their Acyclic Nucleoside Analogues


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Abstract- New paracetamol derivatives and their N-substituted acyclic nucleoside analogues were prepared. The synthesized compounds were tested for their antimicrobial activity against Escherichia coli, Staphylococcus aureus, micrococcus, salmonella typhi and salmonon para typhi. The synthesized compounds were tested also against fungi species such as aspergillus flavus, aspergillus fumigates, aspergillus ochraceus and candida albicans. Most of tested compounds exhibited moderate to high antimicrobial activity while few compounds were found to exhibit little or no activity against the tested microorganisms.

Index Terms- paracetamol derivatives, sugar hydrazones, acyclic nucleosides, antimicrobial activity.

I. INTRODUCTION

Paracetamol (N-acetyl-p-aminophenol or acetaminophen or 4-aminoo-acet) phenol has been used as an analgesic and antipyretic drug since more than six decades. It has been proved as an excellent and effective medication for the pain relief and control of fever in adults and children. However, the overdoses of paracetamol can lead to accumulation of toxic metabolites, causing severe and sometimes fatal hepatotoxicity and nephrotoxicity. Therefore, there has been a concerned search for the discovery and development of newer pharmacological active paracetamol derivatives. The synthesis of newer paracetamol derivative is in need of time. The development of new drugs is one of the fundamental goals in medicinal chemistry. Literature surveyed revealed that various paracetamol derivatives have been synthesized, such as acyl-ether derivatives, nitroparacetamol, 4-(2,3-epoxy-propyl) acetaminophen, polymeric derivative of 4-[6-(methacryloyloxy)hexyloxy]acetanilide, 2-(2-carboxyphenylsulfanyl)-N-(4-substituted phenyl)acetanilide derivatives and dimer of paracetamol. Varying substituent is a common method for drug design in medicinal chemistry. We aimed to synthesize new condensed paracetamol derivative and to test the analgesic and antipyretic activity by in-vivo test. The simple, efficient, sensitive, accurate and economical analytical technique for quantification of such newly synthesized derivatives is needed in pharmaceutical pasture. The development of novel techniques was used for the estimation of drug in different in-vitro and in-vivo pharmacological parameters such as, in pharmacokinetics, pharmacodynamic and bioequivalence study. The number of methods has been reported for the determination of paracetamol, such as flow injection method, liquid chromatography, titrimetry, capillary electrophoresis, chemiluminiscence, electrochemical techniques and spectrophotometric methods. Spectrophotometric methods are mainly based on nitration, oxidation and hydrolysis to paminophenol followed by diazotization and phenolic coupling. Paracetamol in biological fluids (blood, plasma, urine) is mainly determined by HPLC techniques, electrochemical method and spectrofluorimetry, but there are very few spectrophotometric methods are known for determination of paracetamol in biological fluids. The present work describes the synthesis of new paracetamol derivative; [di(4-amino-N-acetyl)phenoxy]methyl ketone (DPMK). The DPMK was synthesized by condensation reaction of synthesized (4-amino-N-acetyl) pheno acetyl chloride (APAC) and (4-amino-N-acetyl)pheno. This derivative has been screened for their analgesic and antipyretic activities. A new spectrophotometric method based on nitrosation reaction was developed for quantitative determination of synthesized DPMK. This method was successfully applied in biological fluids (blood and urine).

Apparent molar volumes and viscosity B-coefficients for paracetamol in aqueous sodium malonate solutions were determined from solution densities and viscosities measured at T = (298.15 to 318.15) K and at pressure p = 101 kPa as a function of paracetamol concentrations. poly(Nile blue) modified glassy carbon electrode (PNBMGCE) was fabricated by electropolymerisation of Nile blue (NB) monomer using cyclic voltammetry (CV) and was used for the determination of paracetamol (ACOP), tramadol (TRA) and caffeine (CAF). A novel voltammetric sensor, butyl-3- methylimidazolium bis(trifluoromethylsulfonyl) imide ([bmin] NTF2) based carbon ionic liquid paste electrode (CILPE) with graphene/multiwall carbon nanotube (GR/MWCNT) hybrid composite as a modifier was fabricated and it was used for simultaneous determination of carbamazepine (CBZ) and paracetamol (PA) for the first time. The cocrystallization of antipyretic drug, paracetamol (PCA) with coformer 5-nitroisophthalic acid (5NIP) have been successfully prepared using solvent evaporation method. Paracetamol, a drug with analgesic and antipyretic properties, is one of the most used substances in human therapeutics, being also frequently detected in aquatic environments. Recent studies report its toxicity towards aquatic species, but the overall amount of data...
concerning its effects is still scarce. Global changes, likely alterations in a biotic conditions, including salinity, can modulate the interactions of contaminants with biota, conditioning the toxicological responses elicited also by pharmaceuticals.\textsuperscript{34}

II. RESULTS AND DISCUSSION

Paracetamol (1) was allowed to react with ethyl chloroacetate in acetone and dry potassium carbonate to afford ethoxycarbonylmethylparacetamol (2) in 85\% yield. Hydrazinolysis of the ethyl ester 2 in ethanol at reflux temperature afforded the corresponding hydrazide 3 in 90\% yield which was allowed to react with diethylmalonate in dioxane at reflux temperature and in the presence of triethyl amine to afford 2-Paracetamolylacetylpyrazolidine-3,5-dione (4) in 79\% yield. Treatment of 4 with the appropriate aldonopenosides (D-xylose and D-Galactose) sugar derivatives in acetone at reflux afforded the corresponding sugar hydrazones 7,8 in 88-90\% yields. Acetylation of 7,8 using acetic anhydride in pyridine at room temperature gave the corresponding acetylated derivatives 9,10 in 87-93\% yields. Treatment of 4 with the aromatic aldehyde derivatives 11-13 in ethanol and in the presence of acetic acid as a catalyst under reflux afforded the corresponding arylidines 14-16 in 87-90\% yields. Treatment of 4 with amine derivatives (2-aminoanaphthol and 2-aminothiazole) in the present of hydrochloric acid and sodium nitrite at room temperature to afford azo-dye derivatives in 70-72\% yields. Treatment of 3 with acetic and/or formic acid under reflux afforded 19, 20 in 90-92\% yields. Treatment of 20 with aromatic amine derivatives 21-23 in absolute ethanol and in the presence of acetic acid as catalyst under reflux to afford the corresponding arylidines 24-26 in 75-80\% yields.

III. EXPERIMENTAL

Melting points were determined with a Kofler block apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer model 1720 FTIR spectrometer for KBr discs. NMR spectra were recorded on a Varian Gemini 200 NMR Spectrometer at 300 MHz for \textsuperscript{1}H NMR with TMS as a standard. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F 245. Elemental analyses were performed at the Microanalytical data centre at Faculty of science, Cairo University, Egypt.

Ethoxycarbonylmethylparacetamol (2)

A mixture of paracetamol 1 (15.1g, 0.1 mole), dry acetonitrile (300 ml), anhydrous K$_2$CO$_3$ (13.8 g, 0.1 mole) and ethyl chloroacetate (15.92 g, 0.13 mole) was heated under reflux for 5h (TLC). The reaction mixture was filtered off and the filtrate was evaporated under reduced pressure. The residue was recrystallized from ethanol to yield white needles in 85\% yield, m.p. 158-160\°C. Rf = 0.48 (5\% MeOH in CH$_2$Cl$_2$). \textsuperscript{1}H NMR (DMSO-d$_6$): δ = 1.17 (t, 3H, $J = 8.1$ Hz, CH$_3$CH$_2$), 2.01 (s, 3H, CH$_3$), 4.11 (q, 2H, $J = 8.1$ Hz, CH$_2$CH$_2$), 4.71 (s, 2H, CH$_2$), 6.83 (d, 2H, $J = 5.5$Hz, H-2), 7.46 (d, 2H, $J = 5.5$ Hz, H-3), 9.79 (brs, 1H, NH).

Paracetamolacetic acid hydrazide (3)

A mixture of 2 (2.37\,g, 0.1 mole), hydrazine hydrate (1.5 g, 0.3 mole) and ethanol (30 ml) was heated under reflux for 5h (TLC). The product was filtered off, recrystallized from ethanol to yield white needles in 90\% yield. White needles (90\%, m.p. 145-147\°C Rf = 0.31 (5\% MeOH in CH$_2$Cl$_2$). \textsuperscript{1}H NMR (DMSO-d$_6$): δ = 1.99 (s, 3H, CH$_3$), 4.31 (brs, 2H, NH$_2$), 4.42 (s, 2H, CH$_2$), 6.89 (d, 2H, J= 5.5 Hz, Ar-H), 7.47 (d, 2H, $J = 5.5$ Hz, Ar-H), 9.30 (brs, 1H, NH), 9.79 (brs, 1H, NH).

2-Paracetamolylacetilpyrazolidine-3,5-dione (4)

A mixture of 3 (2.23 g, 0.1 mole), diethylmalonate (1.60 g, 0.1 mole), dioxane (50 ml) and triethyleneglycol (20.2 g, 0.2 mole) was heated under reflux for 70h (TLC). The mixture was poured over (30 g) ice and the precipitate was filtered and recrystallized from ethanol to yield white powder in 79\% yields, m.p. 220-222\°C. Rf = 0.45 (5\% MeOH in CH$_2$Cl$_2$). \textsuperscript{1}H NMR (DMSO-d$_6$): δ = 2.00 (s, 3H, CH$_3$), 4.05 (s, 2H, CH$_2$), 4.56 (s, 1H, CH$_2$), 6.92 (d, 2H, J = 5.5 Hz, Ar-H), 7.48 (d, 2H, $J = 5.5$ Hz, Ar-H), 9.77 (brs, 1H, NH), 10.11 (brs, 1H, NH).

Sugar Derivatives of pyrazolidine-3,5-diones (7, 8)

A mixture of 4 (0.81 g, 2.80 mmol) in absolute ethanol (100 ml), L(-)-arabinose 5 and/or D(+)-galactose 6 (2.80 mmol) in water (15 ml) and acetic acid (0.6 ml) was heated under reflux for 5h (TLC). The excess of ethanol was removed under reduced pressure and the residue was triturated with diethyl ether (20 ml) and the product was filtered off, washed with diethyl ether and recrystallized from ethanol to give 7 and 8 in 88-90\% yields.

2-Paracetamolylacetyl-4-(2,3,4,5-tetrahydroxypentylidene) pyrazolidine-3,5-dione (7)

White crystals (88\%), m.p. 170-172\°C, Rf = 0.33 (10\% MeOH in CH$_2$Cl$_2$). \textsuperscript{1}H NMR (DMSO-d$_6$): δ = 1.99 (s, 3H, CH$_3$), 3.03-3.51 (m, 4H, H-3', H-4', H-5'), 3.78 (m, 1H, H-2'), 4.24 (brs, 1H, OH), 4.53 (brs, 2H, 3OH), 4.77 (s, 2H, CH$_2$), 6.11 (s, 1H, CH), 6.88 (d, 2H, J = 5.5 Hz, Ar-H), 7.48 (d, 2H, $J = 5.5$ Hz, Ar-H), 9.80 (brs, 1H, NH), 10.24 (brs, 1H, NH).

2-Paracetamolylacetyl-4-(2,3,4,5-tetrahydroxypentylidene) pyrazolidine-3,5-dione (8)

White crystals (90\%), m.p. 201-203\°C. Rf = 0.35 (10\% MeOH in CH$_2$Cl$_2$). \textsuperscript{1}H NMR (DMSO-d$_6$): δ=1.99 (s, 3H, CH$_3$), 2.03-3.78 (m, 5H, H-3', H-4', H-5', H-6'), 4.12 (m, 1H, H-2'), 4.74 (m, 2H, 2OH), 4.43 (brs, 1H, OH), 4.53 (brs, 1H, OH), 4.77 (s, 2H, CH$_2$), 4.90 (brs, 1H, OH), 6.11 (s, 1H, CH), 6.88 (d, 2H, J = 5.5 Hz, Ar-H), 7.48 (d, 2H, $J = 5.5$ Hz, Ar-H), 9.80 (brs, 1H, NH), 10.24 (brs, 1H, NH).

Acetylated Sugar Derivatives of Pyrazolidine-3,5-diones (9,10)

To a solution of 7 or 8 (1 mmol) in dry pyridine (10 ml), acetic anhydride (1.02 g, 10 mmol) was added with stirring at room temperature for overnight. The solvent was removed under
reduced pressure and the residue was coevaporated with toluene (3×5 ml) to afford 9, 10 (87-93%) yields.

2-Paracetamolylacetyl-4-(2,3,4,5-tetra-O-acetyl pentylidene) pyrazolidine-3,5-dione (9)
White powder (87%), m.p. 160-163°C Rf = 0.76 (3% MeOH in CH2Cl2). IR (cm^-1): 3470 (NH), 1783 (CO), 1723 (CO), 1640 (CO).

2-Paracetamolylacetyl-4-(2,3,4,5,6-penta-O-acetylhexylidene) pyrazolidine-3,5-dione (10)
White crystals (93%) m.p. 130-132°C. Rf = 0.70 (3% MeOH in CH2Cl2). ^1H NMR (DMSO-d6): δ = 1.29 (s, 3H, CH3), 2.00 (s, 15 H, 5 AC), 4.29 (s, 2H, CH2), 6.29 (s, 1H, CH), 6.89 (d, 2H, J = 5.5 Hz, Ar-H), 7.49 (s, 1H, CH), 9.81 (brs, 1H, NH), 10.24 (brs, 1H, NH).

2-Paracetamolylacetyl-4-(5-methylfuran-2-yl)methylene]pyrazolidine-3,5-dione (14)
Yellow crystals (87%), m.p. 243-245°C. Rf = 0.72 (5% MeOH in CH2Cl2). ^1H NMR (DMSO-d6): δ = 1.99 (s, 3H, CH3), 2.00 (s, 1H, CH), 4.59 (s, 2H, CH2), 6.89 (s, 1H, CH), 6.91-7.47(m, 7H, Ar-H), 6.88 (d, 2H, J = 5.5 Hz, Ar-H), 7.49 (d, 2H, J = 5.5 Hz, Ar-H), 9.80 (brs, 1H, NH), 10.24 (brs, 1H, NH).

2-Paracetamolylacetyl-4-[4-(4-methyl) benzylidene] (26)
Brown powder (70%), m.p. >300°C. Rf = 0.33 (5% MeOH in CH2Cl2). ^1H NMR (DMSO-d6): δ = 2.00 (s, 3H, CH3), 4.55 (s, 2H, CH2), 6.91-7.47 (m, 7H, Ar-H), 6.88 (d, 2H, J = 5.5 Hz, Ar-H), 7.49 (d, 2H, J = 5.5 Hz, Ar-H), 9.92 (brs, 1H, NH), 10.24 (brs, 1H, NH).

2-Paracetamolylacetyl-4-[4-azopyrazolidine-3,5-dione (17)
Yellow powder (92%), m.p. 157-159°C. Rf = 0.45 (5% MeOH in CH2Cl2). ^1H NMR (DMSO-d6): δ = 1.99 (s, 3H, CH3), 2.00 (s, 1H, CH), 4.59 (s, 2H, CH2), 6.91 (d, 2H, J = 5.5 Hz, Ar-H), 7.49 (d, 2H, J = 5.5 Hz, Ar-H), 9.92 (brs, 1H, NH), 10.24 (brs, 1H, NH).

General procedure for preparation (19, 20)
A mixture of the hydrazide 3 and acetic or formic acid was refluxed for 4h (TLC). The reaction mixture was poured on ice and the precipitate was filtered off, washed with water and dried to give 19, 20 in 90-92% yields.

(Paracetamolylacetyl)formylhydrazide (20)
White powder (92%), m.p. 157-159°C. Rf = 0.45 (5% MeOH in CH2Cl2). ^1H NMR (DMSO-d6): δ = 1.99 (s, 3H, CH3), 2.00 (s, 1H, CH), 4.59 (s, 2H, CH2), 6.91 (d, 2H, J = 5.5 Hz, Ar-H), 7.49 (d, 2H, J = 5.5 Hz, Ar-H), 9.92 (brs, 1H, NH), 10.24 (brs, 2H, NH, CHO).

(Paracetamolylacetyl) Arylidines Derivatives (24-26)
To solution of 20 (10 mmol) in absolute ethanol, different aromatic amines (10 mmol) were added and then glacial acetic acid (1 ml) was added to the reaction mixture which refluxed for 14h (TLC). The solvent was evaporated or concentrated under reduced pressure and the product was filtered off to afford 24-26 (75-80%) yields.

Preparation of Azo-Dye Derivatives (17,18)
A mixture of aromatic amines and hydrochloric acid was stirred in ice bath for 10 min then the solution of sodium nitrite (0.96 g, 10 mmol) was added dropwise to the reaction mixture and then 4 (2.91 g, 10 mmol) was dissolved in ethanol and added dropwise to the last mixture which was stirred at 0°C for 20 min to afford 17 and 18 in 70-72% yields.
White crystals (75%), m.p. 243-245°C. Rf = 0.72 (5% MeOH in CH2Cl2). 1H NMR (DMSO-d6): δ = 1.99 (s, 3H, CH3), 2.04 (brs, 1H, NH), 2.35 (s, 3H, CH3), 4.60 (s, 2H, CH2), 7.23 (s, 1H, CH), 6.97-7.51 (m, 9H, Ar-H), 7.50 (brs, 1H, NH), 8.00 (brs, 1H, NH).

IV. ANTIMICROBIAL TESTING

Antimicrobial screening

The agar diffusion method reported by Cruickshank et al [41] was used for the screening process. The bacteria and fungi were maintained on nutrient agar and Czapek’s-Dox agar media, respectively. The assay medium flasks containing 50 ml of nutrient agar for bacteria and Czapek’s-Dox agar medium for fungi respectively were allowed to reach 40-50 oC to be inoculated with 0.5 ml of the test organism cell suspension. The flasks were mixed well and poured each into a Petri dish (15 x 2 cm) and allowed to solidify. After solidification, holes (0.6 cm diameter) were made in the agar plate by the aid of a sterile cork pooper (diameter 6 mm). The synthesized target compounds were dissolved each in 2 ml DMSO. In these holes, 100 µl each of the compound was placed using an automatic micropipette. The Petri dishes were left at 5 °C for 1 h to allow diffusion of the samples through the agar medium and retard the growth of the test organism. Plates were incubated at 30 oC for 24 h for bacteria and 72 h of incubation at 28 oC for fungi. DMSO showed no inhibition zones. The diameters of zone of inhibition were measured and compared with that of the standard and the solvent alone was used as negative control, the values were tabulated. Ciprofloxacin [42,43] (50 µg/ml) and Nystatin [44] (50 µg/ml) were used as standard for antibacterial and antifungal activity respectively. The observed zones of inhibition are presented in Table 1 and Table 2.

The synthesized compounds were screened in vitro for their antimicrobial activities against *staphylococcus aureus* (G+ve bacteria), *micrococcus* (G+ve bacteria), *salmonella typhi* (G-ve bacteria) and *Escherichia coli* (G-ve bacteria) in addition to strains of fungal species *aspergillus flaus*, *aspergillus fumigates*, *aspergillus ochraceus* and *candida albicans* which were isolated from milk and milk products. The diameters of zone of inhibition were measured and compared with that of the standard and the solvent alone was used as negative control. The values of minimal inhibitory concentrations (MICs) of the tested compounds are presented in Table 1 and Table 2. The MIC values of the results obtained revealed that compounds showed varying degrees of inhibition against the tested microorganisms. The results indicated generally that tested compounds did not show high activity against fungi under test except 17 that exhibited high antifungal activities against *aspergillus fumigates and candida albicans* and some antifungal activity against *aspergillus flaus*, in addition to 18 that exhibited some antifungal activities against *candida albicans*. Also the results indicated that among the compounds tested in antibacterial screening, 9, 15 and 16 exhibited good antibacterial activities in addition to Compounds 14, 15, 19 that exhibited appreciable activity against *micrococcus*. Compounds 2, 7, 8, 9, 10 and 14 exhibited mild to moderate antibacterial activity against *salmonella para typhi*. Compounds 15, 16, 18, 19, and 20 exhibited notable antibacterial activity against *salmonella typhi*. Compounds 2, 10, 14 and 16 exhibited notable antibacterial activity against *Escherichia coli* followed by compounds 9, 17. Compounds 8, 17, 18 and 20 exhibited notable antibacterial activity against *staphylococcus aureus*.

REFERENCES


AUTHORS

First Author – Author name, qualifications, associated institute (if any) and email address.
Second Author – Author name, qualifications, associated institute (if any) and email address.
Third Author – Author name, qualifications, associated institute (if any) and email address.
Correspondence Author – Author name, email address, alternate email address (if any), contact number.
Scheme 1
Scheme 2

\[ 4 + R_1\text{CHO} \xrightarrow{\text{AcOH, ethanol/reflux}} 5,6 \]

\[ \text{AcO}_2/\text{pyridin, stirring} \]

\[ R_1 = \]

\[ \text{D-}(+)\text{xylose} 5,7 \]

\[ \text{D-}(+)\text{Galactose} 6,8 \]

\[ \text{D-}(+)\text{xylose} 9 \]

\[ \text{D-}(+)\text{Galactose} 10 \]
4 + RCHO $\xrightarrow{\text{AcOH, ethanol/reflux}}$ R

11, 14 = 5-methylfuran
12, 15 = 4-flurophenyl
13, 16 = 4-N,N dimethylaminophenyl

Scheme 3

4

(i) $\xrightarrow{\text{N,N-dimethylaniline, HCl, NaNO2}}$

(ii) HCl
(iii) NaNO2

(i) $\xrightarrow{\text{1,3-dimethylbarbituric acid, HCl, NaNO2}}$

Scheme 4
Scheme 5

\[
\begin{align*}
\text{Scheme 6}
\end{align*}
\]
Table (1) Minimum inhibitory concentrations (MIC in µg/ml) of the title Compounds against bacteria species. The negative control DMSO showed no activity.

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Table (2) Minimum inhibitory concentrations (MIC in µg/ml) of the title Compounds against fungi species. The negative control DMSO showed no activity.

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